MEETING

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OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PROPOSITION 65

CARCINOGEN IDENTIFICATION COMMITTEE

SACRAMENTO CITY HALL

915 I STREET

CITY COUNCIL CHAMBERS

SACRAMENTO, CALIFORNIA

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ALSO PRESENT

Mr. Stanley Landfair, McKenna, Long & Aldridge

Dr. Linda Malley, DuPont

Dr. J. Morel Symons, DuPont

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PROCEEDINGS

DIRECTOR DENTON: Good morning. I'd like to call the meeting to order. So If everyone would take their seats.

Good morning to everyone. We appreciate the panel members and the audience appearing at 9:30 post-election day. I'm sure there are a few people that are sleep deprived, including myself. But I wanted to tell Dr. Mack that he is sitting in the chair of our new mayor. He is the first person to sit in the chair of our new mayor.

(Laughter.)

DIRECTOR DENTON: Yeah, former NBA star, Kevin Johnson. Someone said that he might come by this morning, and I said I didn't think so.

(Laughter.)

DIRECTOR DENTON: At any rate, this is a meeting of the Prop 65 Carcinogen Identification Committee. And I want to make some quick introductions, and then I will turn the meeting over to Dr. Mack.

To my left is Dr. Mack, the Chair of the Committee. Next to him is Dr. Marty Hopp, then Dr. Joe Landolph, and then Dr. David Eastmond. To my right, Dr. Anna Wu, then Dr. Solomon Hamburg. And to his right is Dr. Darryl Hunter.

So welcome to you all.

I think all of you have copies of the agenda. The agenda and the handouts and the overheads and the PowerPoint presentations and the sign-up sheet are all available when you came in.

So with that I think, knowing that we have two items on the agenda plus some staff discussions for the panel, I will turn it over to Dr. Mack.

CHAIRPERSON MACK: This, of course, is new technology, and it's going to take me awhile to get used to it.

It's nice to see all of your enthusiastic faces sitting there. So there must be a lot of other people who are sitting dejected somewhere else. But that's okay.

(Laughter.)

CHAIRPERSON MACK: Who is the staff person that's going to take the lead on the first compound, which is N,N-Dimethylformamide?

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Dr. Mack, that will be Lindsey Roth and David Morry.

CHAIRPERSON MACK: Thank you.

All right, Martha. Let them proceed.

(Thereupon an overhead presentation was Presented as follows.)

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Okay.

MS. ROTH: Okay. Is this close enough?

DIRECTOR DENTON: I think you have to turn yours off.

MS. ROTH: Is this all right?

All right. Oh, who's shaking their head no?

All right. Is this okay?

All right. Today, we're going to discuss the evidence of carcinogenicity for Dimethylformamide or DMF.

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MS. ROTH: All right. We see here the physical and chemical data for this solvent.

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MS. ROTH: DMF is used in a variety of industries. Studies in aircraft repair, leather tanning, and manufacture of acrylic fibers and tint of plastic sheeting will be discussed here.

The U.S. production volume -- the non-confidential U.S. production volume was estimated to be 100 to 500 million pounds in 2002. And the air emissions in California for 2006 reporting year were estimated to be 5.6 tons under the California Toxics Inventory.

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MS. ROTH: All right. For the carcinogenicity studies in humans, there were studies in two industries, a cluster investigation in each, leather tanners and Navy F4 aircraft repairmen, and a case-control and cohort study follow-up in the leather tanners. There were also studies of case-control and cohort at DMF production and use facilities among workers there.

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MS. ROTH: There are also studies in animals. There's an older drinking water study in rats. There are also two sets of long-term inhalation studies in male and female mice, and two sets of long-term inhalation studies in male and female rats.

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MS. ROTH: The original cluster started with testicular germ cell tumors among Navy F4 aircraft repairmen. There were 3 males with -- of cases among 153 workers at one facility. And the investigation found four more cases at another F4 repair facility. There were no cases at a third facility where there was no DMF exposure.

The cases were exposed for 4 to 19 years. And the repairmen dripped a solvent mixture containing 80 percent DMF onto cables and resulted in dermal and air exposures that were likely.

There were no DMF air measurements. But Frumin,

et al., speculated that the exposures -- the air exposures were greater than 10 ppm.

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MS. ROTH: Another cluster investigation was performed with the same type of testicular germ cell tumors at a leather tannery and found three cases. These men were exposed for 8 to 14 years. They worked on a spray line where they spread dyes on leather using paddles while leaning close to the hide, resulting in dermal and air exposures.

There were no DMF air measurements. But Frumin speculated that the air exposures were greater than 10 ppm before being removed from the process.

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MS. ROTH: A follow-up study was conducted, a case-control study by Frumin, in the whole county that the leather tanner cases were found. And the cases were obtained from the New York State Cancer Registry and were diagnosed with testicular germ cell tumors from 1974 to 1987. This resulted in seven additional cases, for a total of ten in the county.

The control group consisted of 129 men who developed another type of cancer during the same years. And 50 percent of the cases and 13 percent of the controls were in leather-related occupations. This resulted in an

odds ratio of 5.8, significant when compared against 1.

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MS. ROTH: Brought to our attention by comments from DuPont, there is a nonpublished report from New York State Department of Health, and it reported the same information as the Frumin study. There was a slightly larger control group, but it included a description and discussion of the controls and cases that was not in the Frumin paper. Many controls were missing occupation information and therefore removed from the analysis. And this was more prevalent among younger controls.

Because the controls were obtained from other cancer diagnoses, the controls were likely older -- were older than the cases, less likely to have testicular germ cell cancer, and therefore potentially overestimates the risk of testicular cancer.

But the authors mention that there may be -- percent of leather tanners may be high in the controls in comparison to the cases and therefore potentially obscure the effects from leather tanning occupational exposure. This results in a potential bias in an unknown direction.

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MS. ROTH: A follow-up study of the leather tanners, a cohort study this time at the leather tannery consisting of 80 workers. The expected number of cases

were calculated using New York State cancer incidence rates and person-years at risk from 1975 to 1987. The Standardized Incidence Ratio was significant at 40.5 when compared against 1.

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MS. ROTH: At the DMF production and use facilities studies, there was two: A cohort study by Chen involving one plant with the manufacture of acrylic fibers; and a case control study by Walrath that involved four plants, one DMF production plant and three manufacturing plants including the cohort from above.

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MS. ROTH: Here is some information about the different plants. Plant C is the cohort study by Chen. And we notice there are different exposures by plant; and this includes the type of facility, the percent of workers exposed, and the average DMF levels.

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MS. ROTH: In the cohort study, the plant manufactures acrylic fibers. There was acrylonitrile co-exposures for some employees. And acrylonitrile is a known carcinogen. This involved two cohorts that are not used for the DMF study -- or the DMF consideration.

There was also a DMF-only cohort where the workers were not exposed to acrylonitrile and then a

cohort where workers were exposed to neither acrylonitrile or DMF.

Cancer cases were obtained from the DuPont Cancer Registry. And they were cancers that were diagnosed only while the employees were employed at DuPont.

There is 47 cancer cases among 2,530 exposed for the DMF-only cohort, and 17 cancer cases among 1,130 unexposed in the control cohort that did not have DMF or acrylonitrile exposures.

The exposure classification was grouped as "ever" versus "never" and occurred between 1950 and 1970.

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MS. ROTH: All right. The expected counts were based on the internal DuPont cancer incidence rates and resulted in one significant association in the DMF-only cohort. This was the buccal cavity and pharynx. And the authors broke down the employees by payroll class. So we see that it was significant for the wage category, but not the salary category. But it was also significant in the combined group. There are confounding exposures of alcohol and smoking for this particular endpoint.

Other cancers were examined but reported no significant associations in the paper.

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MS. ROTH: Using National Cancer Institute's

Surveillance Epidemiology End Results cancer incidence rates also resulted in some significant associations.

The buccal cavity and pharynx, which was nine cases, had significantly higher than expected association with the expected 3.3 cases. The authors note that six of the cases had high exposure and three of the cases had moderate exposure to DMF.

Malignant melanoma was also significant using these expected cancer incidence rates, with 5 cases compared against 1.6 expected. And all five of these cases were in the high DMF exposure category.

The expected counts with SEER rates were not significant for the other cancers in this cohort and were not provided.

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MS. ROTH: In the case control study by Walrath, four plants were included, the three manufacturing and the one production. The cases were also obtained from the DuPont Cancer Registry from employees diagnosed while employed at DuPont.

Co-exposure to acrylonitrile was not discussed, even though we know it occurred in Plant C.

Controls were matched by plant, age, sex, and payroll type. The activities varied by plant. And plant was used as a surrogate of exposure.

The five cancers examined were buccal cavity and pharynx, liver, prostate, testis, and skin.

The odds ratio was reported by plant as well as the combined odds ratio for all plants.

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MS. ROTH: There was a small number of cases for each cancer in this particular study. Prostate cancer, which had four cases at Plant D, was the only significant association, with an odds ratio of 8.

The authors also noted that there was a logistic regression trend from malignant melanoma by increasing exposure category.

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MS. ROTH: There are exposure differences between the different industries. And this could be informative about the end results -- the end cancer results. There was dermal and air exposure in leather and aircraft repair industries. And dermal exposure is relatively unknown in the production use facilities.

A study examined the body burden of DMF using two urinary biomarkers, DMF and a metabolite, NMF. And they examined -- or took measurements using personal air and dermal DMF measurements in several occupational industries, including synthetic leather, which has significant air and dermal exposure, and a copper laminate

circuit board industry, which had air exposure only.

And there was a one-day study to examine the effect over one day and a one-week exposure study to examine the cumulative effect over one week.

Higher levels of the metabolite, NMF, for the workers with dermal exposure was found. And the authors conclude that dermal DMF exposure results in bioaccumulation.

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MS. ROTH: For the analysis of Chen. Chen reported using a Poisson distribution with two tails and a .1 cutoff. When using the Poisson distribution using a .1 cutoff with one tail and a -- I'm sorry -- a .1 cutoff with two tails and a .1 cutoff -- I'm sorry -- .05 cutoff with one tail is identical.

It was unclear why some of the associations reported in the publication were not significant and they were not reproducible.

In comments received from DuPont after releasing the HID, it was mentioned that Standardized Incidence Ratios were used to calculate the effects. But Standardized Incidence Ratios, or SIRs, were not mentioned in the publication and not reported in the tables. And this includes both the effect level, confidence intervals, or P-values.

There are -- if a Standardized Incidence Ratio is used, there are -- you can calculate a confidence interval or there are two distribution methods to see if the SIR is significantly different from one. One is the Poisson distribution, which has the mean of the distribution as the expected count. And then we're interested in the probability of an observed count or greater. A priori, this is testing the association of cancer with DMF, in that, we aren't interested if it prevents cancer. So one tail assumption is appropriate. The authors, Chen, et al., in fact say, in quotes, "The initial objective of this study was to determine whether exposure to DMF and acrylonitrile, separately or in combination, was associated with higher-than-expected cancer incidence."

Another distribution method is the chi-squared distribution with expected counts greater than two. And this is inherently two tailed.

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MS. ROTH: Both of these distribution approaches provide qualitatively similar results.

The significant associations in the DMF-only cohort were buccal cavity and pharynx and the stomach for the Poisson distribution using the DuPont expected rates. However, from malignant melanoma, it was only significant using the SEER expected counts.

With a chi-square distribution we find significant associations for the buccal cavity/pharynx, malignant melanoma, prostate and stomach.

Based on the methods described in the paper, additional significant associations are found. In fact, the confidence intervals provided by DuPont in the comments have a change of significance on several endpoints, six total in both directions, and are noted with footnotes in their appendix.

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MS. ROTH: All right. Here is the observed and expected counts with P-values for the chi-square distribution. And this was used to try to replicate the results in the paper and see why some associations were significant and others were not.

You can see with the chi-square approach, the buccal cavity and pharynx, malignant melanoma, prostate and stomach were all significant in at least one of the wage categories -- or payroll categories.

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MS. ROTH: With the Poisson distribution we see very similar results. The malignant melanoma in the wage category, which -- whoops -- right here was significant when SEER rates were used instead of the DuPont internal rates. And we see that the malignant melanoma for wage

and the prostate for salary, which were significant for Poisson, are close to being significant.

In fact, with this limited cancer registry, one or more cases could increase the statistical power and likely bump some associations to being significant.

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MS. ROTH: All right. The limitations. There were limitations in all of the Epi studies. Specifically, for Navy F4 and leather tanning workplaces the DMF exposure was not quantified.

In the DMF production and use facilities there was a very limited cancer registry where cases were from only employees diagnosed while employed. And this resulted in a limited number of cases.

There was truncated follow-up.

The data collected on duration and intensity of DMF exposure was not used in most analysis. And, in fact, they were matched -- the controls and, depending on the study, were matched on plants, and DuPont's internal incidence rates were used for comparison.

There was limited statistical power in these studies, and the results were unable to be reproduced.

There is confounding exposures in all of the studies -- all of the Epi studies. Workers were exposed to many chemicals along with DMF in the leather tanning

and aircraft repair. There were also co-exposure to acryonitrile that was not addressed in the case control study of the production and use facilities. And other non-acryonitrile exposures were addressed in either of the production and use facilities studies.

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MS. ROTH: So there are exposure differences among the industries, and this may explain the variable findings in cancer.

Higher levels of DMF were likely in the Navy F4 repair and leather tanning occupations.

Dermal exposure was associated with bioaccumulation of DMF. And this is especially likely in the leather tanning and aircraft repair industries.

Air level experience in the production and use facilities were all fairly low, with an average air concentration of less than 10 ppm.

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MS. ROTH: So, in conclusion:

There were clusters of testicular germ cell tumors in two distinct occupationally exposed groups.

Case control and cohort studies of leather tanners found an association of testicular germ cell tumors among workers exposed to DMF.

There is some evidence of cancer risk among DMF

production and use workers.

But definitive well-conducted studies are needed.

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DR. MORRY: Okay. Let's go onto the animal studies -- is this working good? -- go onto the animal studies of testing of Dimethylformamide in mostly rodents.

First, there was a drinking water study that was done in '67. It's a very brief report in a German journal. And this -- it was a small number of rats that were given up to -- given Dimethylformamide in drinking water up to a total dose of 37 milligrams per kilogram body weight. And they did not observe any tumors in this study.

Then we have two sets of studies -- inhalation studies in mice.

First, there was a study by Malley, et al., from DuPont who did male and female CD-1 mice exposed to doses of 0, 25, 100, and 400 ppm for 18 months.

And then later there was a study by Senoh, et al., from Japan who did a study again in male and female mice, this time a different strain BDF1 mice. And they did 0, 200, 400 and 800 ppm. And the length of the experiment was for 24 months.

There were also some rat studies, which I'll mention later on.

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DR. MORRY: Okay. To look at the mouse studies, first of all Malley, et al.:

They found no effect on survival in either male or female mice.

The body weights increased in both male and female mice for the top dose group, the 400 ppm.

There were increased liver-to-body weight ratios in the 100 and 400 ppm males and in the top dose females.

They observed centrilobular hepatocellular hypertrophy and hepatic single-cell necrosis at the two highest doses in both sexes. So these are indications of toxicity to the liver.

They observed no treatment-related increase in tumor incidence at the P less than .05 level. There were tumors, but there were not a statistically significant increase over the controls.

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DR. MORRY: The Senoh, et al., studies -- more recent studies in mice:

Again, they found no effect on survival in either sex.

The growth was suppressed in the exposed groups.

The liver-to-body weight ratio increased with exposure in all the exposed male and female mice.

Again, centrilobular hypertrophy, and they observed nodules in the exposed mice of both sexes.

They observed hepatocellular adenomas and carcinomas which were statistically increased in male and female mice in the exposed groups.

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DR. MORRY: So here's the data from the Senoh study.

And we see that for hepatocellular adenomas, there's statistically significant increases at the 200, 400 and 800 dose levels, with a high statistical significance by pairwise comparison. And there's very high statistical significance for the trend test.

Likewise, with carcinomas, statistically significant in all the exposed groups by pairwise comparisons using the Fisher exact test. Also, for hepatoblastoma.

And then when you combine all the tumors, it's highly statistically significant by pairwise comparison at all the exposed levels, not just the top dose, at the same levels that were the top -- at the same level that was the top level in the Malley study and a highly significant trend test. This is for the male mice.

When we look at the female mice, we see similar results, statistically significant by pairwise comparison

for both adenomas, carcinomas, not for hepatoblastomas. And then when you combine the tumors, highly statistically significant trend test and statistically significant increases at all three exposure levels by pairwise comparison.

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DR. MORRY: Okay. There were two sets of rat studies: A male and female CD rats exposed at 0, 25, and 100, and 400 ppm for two years. And this, again, is Malley, et al. And, again, there was a Senoh study of rats, male and female, F344 rats exposed to 0, 200, 400, and 800 ppm, again for two years. So the same dose levels as in the mouse experiment.

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DR. MORRY: Survival was not affected by DMF treatment in the rats in the Malley study. Body weights were reduced in male rats exposed to 100 and 400 and in female rats exposed at the top dose. There were relative liver weight increased in the male and female rats exposed at the 100 and 400 ppm levels. They saw centrilobular hepatocellular hypertrophy in all the exposed groups in both sexes. But they saw no treatment-related increase in tumor incidence at the .05 level.

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DR. MORRY: The Senoh, et al., study was similar.

Survival was unaffected in male rats. There was a reduced survival in female rats exposed at the highest dose level due to liver necrosis. And body weights were reduced in both sexes at the 800 ppm dose. There was an increase in liver-to-body weight ratios in the rats of both sexes at all exposure levels.

Centrilobular necrosis was seen in both sexes at the highest dose, but it was significant only in the female rats.

And, again, tumors were found at statistically significant levels. Hepatocellular adenomas and carcinomas were increased in both male and female rats. I should mention that all these experiments, both the Malley and the Senoh studies, were done according to OECD guidelines.

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DR. MORRY: So here's the data for the male rats in the Senoh, et al., study. We see statistically significant increases in adenomas at the 400 and 800 ppm levels was a highly significant trend. Increase in carcinomas statistically significant at the 800 ppm level, highly significant trend test. And the combined tumors we see increases statistically significant at both the 400 and 800 ppm exposure levels and a highly significant trend.

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DR. MORRY: For the female rats, we have statistically significant increases in adenomas and carcinomas and statistic -- also significant by the trend test and statistically significant when the tumors are combined, both by pairwise comparison at the high-dose level and by the trend test.

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DR. MORRY: So the conclusions we can draw from the animal studies are that, as I mentioned before, there were no tumors seen in the drinking water study by Druckrey, et al. There were hepatocellular adenomas and carcinomas, which increased with the positive trend in both male and female BDF1 mice in the Senoh study. Hepatocellular adenomas and carcinomas also increase with the positive trend in male and female F344 rats in the Senoh study. There were no treatment-related tumor increases observed in the studies in mice and rats by Malley, et al.

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DR. MORRY: So the differences between the two studies -- since the results are so different, we might wonder what the differences might be that would account for those. They differed in several ways. One was, for the mouse study there was a difference in the duration.

The Malley study was only for a year and a half; the Senoh study was a two-year study.

The highest dose was different. The Malley highest dose was 400 ppm and the Senoh highest dose was 800 ppm. But keep in mind, that the Senoh study saw increases in tumors also at 400 ppm and the Malley study did not.

The strains of animals that were used were different:

Mice: The Malley study used CD-1 mice; the Senoh study uses BDF1 mice.

And in rats: The Malley study used CD and the Senoh used F344.

So there might be some difference in the sensitivity of the strains that could be partly responsible for the different results.

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DR. MORRY: The metabolism of DMF, it is similar in all mammals that have been studied, humans and rodents and cynamologous monkeys. It begins with hydroxylation by CYP2E1 to produce N-hydroxymethyl N-methylformamide, which then, without benefit of an enzyme, loses a formaldehyde molecule and becomes N-methylformamide, which is the NMF that Lindsey was mentioning earlier.

Then the metabolism continues. And at the end

result -- or at the end of the chain, there's a cysteine conjugate, which is formed. And that's a significant metabolite in humans. It's also found in rodents, but to a lesser extent.

So there's some differences between humans and rodents, not in the pattern of this metabolism, but in the amount of the metabolites that may accumulate in tissues. And this is not perfectly understood at this point in time.

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DR. MORRY: So looking at some other relevant data bearing on the carcinogenicity of this chemical, we have genotoxicity data. Dimethylformamide is negative in most experimental systems ranging all the way from bacteria to mice, as reported in IARC. Some evidence of -- there was some evidence of weak genotoxic activity in mouse lymphoma assay; unscheduled DNA synthesis, indicating DNA damage in rat hepatocytes; and clastogenicity in saccharomyces yeast. So there's some positive and some negative in the genotoxicity data.

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DR. MORRY: Now, looking genotoxicity data for humans, we have three studies to look at.

Chromosomal gaps and breaks in peripheral lymphocytes were increased from .4 percent in controls to

1.4 percent in exposed workers in a study by Berger, et al. But these workers were also exposed to methyl amines. So we have a possible confounding factor there.

Chromosomal and aberrations were increased in peripheral lymphocytes of workers exposed to DMF. But these workers were also exposed to trace amounts of other chemicals.

And then the final study -- or the final one on this slide is sister chromatid exchanges were increased significantly in high and medium DMF-exposed groups of women workers in a study by Seiji, et al. And in this study there was no co-exposure. They were exposed only to DMF.

So we have some evidence from humans and some evidence from lower organisms, as they're called.

Other relevant data. Other effects on the liver, we saw in the rodent studies that there were changes in liver-to-body weight ratios. And there were histological changes. So there was hypertrophy, there was centrilobular necrosis, and there were altered cell foci seen in all the studies and rodents. So indicating that DMF is a chemical that's toxic to the liver.

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DR. MORRY: So, thinking about the possible mechanisms of action for DMF, we can't rule out

genotoxicity, since it -- it's not positive in all systems, but it seems to have some genotoxic activity both in humans and in test and in experimental systems.

Another possibility is that through its toxicity to liver cells, it kills liver cells, which then stimulates cell proliferation due to either cytotoxicity or apoptosis of liver cells. That would be another mechanism of action that could make it carcinogenic.

And then there's also an idea that DMF might work by facilitating the permeation of other chemicals into target tissues. A lot of the recently published studies on DMF have to do with its use as a vehicle for carrying drugs into tissues. So apparently DMF is a very good solvent, not only on airplanes but also on people. It can carry drugs into people. So it may facilitate entry of carcinogens into tissues where they would work. And, of course, the mechanism of action could be a combination of any of these and maybe others we haven't thought of.

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DR. MORRY: IARC did a review in 1999, which was before the Senoh, et al., studies were published in 2004. They concluded that there was inadequate evidence of carcinogenicity in humans and suggested -- that the data suggested a lack of carcinogenicity in animals. So they classified it in the Group 3 as not classifiable as to

carcinogenicity in humans.

Keep in mind, of course, that this was before the Senoh results.

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DR. MORRY: So to summarize the evidence for the carcinogenicity of DMF:

In human studies we have limited, but suggestive evidence, from the occupational studies that Lindsey described.

In animals we have hepatocellular adenomas and carcinomas, which were seen at statistically significant levels in both male and female F344 rats.

Then we also have hepatocellular adenomas and carcinomas in male and female BDF1 mice and at statistically significant levels, and also hepatoblastomas at significant levels in the male mice.

And for other evidence, we know that DMF was at least weakly genotoxic in both rodents and humans.

That concludes the talk.

CHAIRPERSON MACK: Thank you very much. We will be having an opportunity to weigh in on our opinions a little bit later. But right now we can ask questions of fact about the material that's been presented.

Do you have any, Marty?

COMMITTEE MEMBER HOPP: Yeah.

Is this on?

I have some questions about the human studies, particularly in the case controls. My concern is the controls in these large number of people for alcohol, cigarette and chaw exposure among the controls and the workers. Can you tell me a little bit more about that?

MS. ROTH: Are you referring specifically to the production and use ones --

COMMITTEE MEMBER HOPP: Yes.

MS. ROTH: -- or the leather tanning?

The production and use?

COMMITTEE MEMBER HOPP: Yes.

MS. ROTH: Yes, that's a -- alcohol and smoking are known to be confounders. And so that could very well be part of what's going on in that particular endpoint.

COMMITTEE MEMBER HOPP: But in looking at those, how were they controlled from the patients who developed tumors versus the case -- the non --

MS. ROTH: I don't believe they were controlled for, but it was mentioned that that was possible.

COMMITTEE MEMBER HOPP: Yeah, that was my impression, that there wasn't any controls in the studies for alcohol or cigarettes use or chaw, and yet the primary tumors that they reported were the buccal mucosa, which is a very common site for chaw and alcohol. And, also, if it

was a solvent you would find that it would be developed in the buccal mucosa.

COMMITTEE MEMBER HOPP: I have another question. Can I go on?

CHAIRPERSON MACK: Anybody else?

COMMITTEE MEMBER HOPP: I had another question.

CHAIRPERSON MACK: Oh, you have another one?

COMMITTEE MEMBER HOPP: Yeah, another question, regarding the animal studies.

Again, these -- since the human studies were more a buccal and pharyngeal tumors, which would suggest more topical or direct toxicity in carcinogen activity as a direct carcinogen as opposed to necessarily a systemic -- a metabolic carcinogen, are there any animal studies where this was just painted on the skin of mice as opposed to being inhaled or being in the drinking water?

DR. MORRY: I don't remember any skin painting studies for DMF. There's been injection studies and, as I mentioned, a drinking water study. The only studies that really reported any significantly -- statistically significant increase in tumors were the inhalation studies.

CHAIRPERSON MACK: Okay. I have a couple questions.

You know, we're very quick to dismiss clusters.

But, in this case, it's much more complicated than a cluster. And I think there's some pieces of information that we ought to get on the record.

First of all, these first two clusters were in Navy men, as opposed to industrial employees. And the presumption that I would have is that their welfare was not probably looked after quite as much as it might have been had they been working in a company. I don't know if that's true or not. But it sounds like that might be true from the way they were distributing the material, because they were just dripping it over objects. Is that fair?

MS. ROTH: Yes.

CHAIRPERSON MACK: Okay. The second question -- and this is really important with respect to clusters -- is how they came to be noticed. The first one -- presumably it almost doesn't make any difference how it came to be noticed, whether it was because of the men themselves or a person in the Navy who noticed it or whatever. But the question I have is, over what period of time did the three cases occur. Do you know?

MS. ROTH: Just a minute.

CHAIRPERSON MACK: And a related question is -- I'm just verifying -- they were all the same cell type of testicular cancer?

MS. ROTH: Yes, all the same cell type.

I believe it was over the short course of a couple years.

CHAIRPERSON MACK: A couple years, ten, or a couple years, three, or --

MS. ROTH: Let's see here. They all occurred between 1981 and 1983.

CHAIRPERSON MACK: Okay. Then the second question is -- the second cluster in the other military facility was uncovered by the epidemiologist who observed or worked on or worked up or investigated the first one. And is it true that he looked at that facility strictly because it was the same kind of exposure circumstances, not because anybody reported cases from that other facility to him independently?

MS. ROTH: Yes. They decided to look at two other facilities, one which is this Navy F4 repair facility that performs the same operation to see if there were cases there; and then the third facility where they found no cases, which did not have the DMF exposure. It was a different type of aircraft that they were repairing so the procedure was different.

CHAIRPERSON MACK: And do we know that those cell types of those four cases in the second facility were also the same as the ones in the first facility?

MS. ROTH: I believe so.

CHAIRPERSON MACK: Martha's coming to your assistance.

MS. ROTH: They're all reported as germ cell.

CHAIRPERSON MACK: Okay. Next question: Over what period of time did those occur?

MS. ROTH: Those occurred from 1970 to 1983.

CHAIRPERSON MACK: Okay. So that's a longer period of time.

MS. ROTH: A little bit longer.

CHAIRPERSON MACK: Okay. Now, the third question is with respect to the cluster among the tanning workers.

Can I presume that that cluster came to the attention of the State of New York in ignorance of the naval clusters? Or did they, in fact, look for it because of the naval clusters?

MS. ROTH: I believe the men were actually working together and found it them -- or maybe -- hold on just a second.

CHAIRPERSON MACK: My recollection is that the people themselves reported it --

MS. ROTH: Yes.

CHAIRPERSON MACK: -- through the union.

MS. ROTH: Yes. Yeah, they worked together on one shift -- it was a night shift. And over the course of finding out they're having the same treatment, they

brought it to the attention of investigators.

CHAIRPERSON MACK: And then the final question relates to the cohort study that was done in that tanning operation in New York. It was said that seven or some proportion of the ten cases -- 50 percent of the ten cases had exposure in the leather industry. Do we know -- now, of course, there's lots of jobs in the leather industry, and some of them may and some of them may not involve DMF. And the question is, do we know any more about the jobs that were involved and whether or not they were likely to have had exposure?

MS. ROTH: No, they -- because of the way that it was determined what their occupation was, it was very general. And it also didn't go back very far. Often it was just the previous -- the previous job. And so there's not more information. And that's the best they could do in the grouping, was to say leather-related occupations.

CHAIRPERSON MACK: Okay. Thanks a lot.

MS. ROTH: You're welcome.

CHAIRPERSON MACK: Does anybody else have any more questions about -- David.

COMMITTEE MEMBER EASTMOND: Well, let me follow up on a couple things.

With regard to the -- I guess these were the pharyngeal/buccal tumors. The public comments had

indicated in the Chen, et al., that all of those had occurred in heavy smokers that had smoked for like 20 years; is that correct?

MS. ROTH: I don't recall if it was all of them, but it was a majority.

COMMITTEE MEMBER EASTMOND: Okay. And that was just one I just wanted clarification.

MS. ROTH: But that also was the study where there were a lot of limitations.

COMMITTEE MEMBER EASTMOND: Okay. The other question has to do with kind of these possible mechanisms of action -- and we'll get to this. But my impression that there were a large number of short-term genotoxicity studies done, something in the neighborhood of 40 or 50. And there were like 4 or 5 that were positive. Is that correct? I mean the IARC tables go on for several pages --

DR. MORRY: The ones that were positive seem to be more in the realm of the -- like clastogenicity, both in humans and the animals. So it seems to be negative usually in mutation assays, but positive for clastogenicity.

COMMITTEE MEMBER EASTMOND: Okay. Thanks.

The other thing is kind of a clarification. The mechanism which I thought was quite intriguing is it

facilitates permeation of other chemicals. That's really only relevant for the human studies. The animal studies are going to be the direct chemical itself, correct?

DR. MORRY: That's probably right. But there's a possibility that there could be some carcinogens lurking around even in a sterile clean laboratory, or they could come from inside the animal itself. Like chemicals that are normally sequestered in one tissue could be facilitated to move to another tissue and could have carcinogenic activity that way.

COMMITTEE MEMBER EASTMOND: One of the things I also found was kind of intriguing was this idea that there was this co-exposure to chromate-type compounds. And that was kind of the ideas, that maybe these were facilitating the penetration of these chromates. The question I had is, are -- do you know if chromates are associated with these sorts of germ cell tumors in humans?

DR. MORRY: I don't know.

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: I'm not aware of that. And Dr. Jay Beaumont is shaking his head, who's reviewed the literature on hexavalent chrome.

MS. ROTH: Back to your first question about the smoking and alcohol. It turns out 11 of the -- all 11 were heavy smokers, but only 2 were heavy drinkers.

COMMITTEE MEMBER EASTMOND: Okay. Thanks.

CHAIRPERSON MACK: Anna.

COMMITTEE MEMBER WU: I have a question about the New York State Cancer Registry case control study. If I read that paper correctly, they interviewed the cases to assess exposure, but they didn't interview the controls. Is that correct?

MS. ROTH: I believe they interviewed as many people as they could. Sometimes they were deceased and so they would interview the families. But, correct, I don't think they were able to interview everybody.

COMMITTEE MEMBER WU: Did they also --

MS. ROTH: But they used -- go ahead.

COMMITTEE MEMBER WU: Did they also mention whether they matched the cases and controls in terms of -- I can't remember what they tried to actually match for. It wasn't very clear. Do you remember? Because I think it was a very heterogeneous group of diagnosis among the controls. But I couldn't tell what they were actually trying --

MS. ROTH: Yeah, I don't see what was matched off the top of my head at the moment.

COMMITTEE MEMBER WU: And they didn't give what percent of controls were actually -- they managed to interview versus using a surrogate. Because the cases,

they actually managed to interview more of them, right?

MS. ROTH: That sounds -- yes.

COMMITTEE MEMBER WU: Okay. Thank you.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Hi. I enjoyed your presentation.

I had a couple of questions. One was for the leather tanners. What other chemicals are in that industry besides DMF? I think chromium is one that's occasionally used. Is that true?

MS. ROTH: I'm not sure about exactly what's used. But they did say, I believe it was in the NIOSH report, that they were moving away from lead-based dye. So I know that lead was possible as well.

COMMITTEE MEMBER LANDOLPH: Okay.

COMMITTEE MEMBER HOPP: I'm sorry. Did they control for aniline dyes when they were looking into it also at that time?

MS. ROTH: I don't recall if they mentioned that. They might have, but not mentioned it.

COMMITTEE MEMBER LANDOLPH: And for the leather tanners, the odds ratio of 5.8, it seems pretty high in the Frumin study and the SIR in the Calavert study is 40.5. So these are pretty big numbers. And I don't know if our epidemiologists would comment on them. But I want

to see if you can make them go away in my mind. I'm not prepared to dismiss them yet. Do you have any doubts about those numbers or any criticisms of them from your point of view?

MS. ROTH: Well, there is the confounding issue of other exposures, the exposure classification. They didn't necessarily have as good of classification as they'd like. But whether that would completely remove the effect, I'm --

COMMITTEE MEMBER LANDOLPH: And are there any other confounding exposures which you think could be ascribed to the tumors that are induced, the testicular tumors, the malignant melanomas, et cetera? Is there anything definitely you could point to that would convince you?

MS. ROTH: Well, besides co-exposures that we've already discussed.

COMMITTEE MEMBER LANDOLPH: Okay. Just one more. And I guess this is more to Dave.

So, Dave, I was struggling with those two different animals, but I think your summary table's very good. It seems to me in the Senoh studies, yes, I agree with you, there was longer exposures, 24 months versus 18. And Senoh pushed it to 800 parts per million versus the 400 that Malley stopped at. And then, in addition,

there's a different genetic background of the rats. And Senoh's had positive in male and female of the mice and the rats they used. And Senoh uses the Fisher 344 rats, which the NTP studies use. So I think I can reconcile, in my mind, the difference between those and still accept the Senoh as positive.

What is your opinion of that?

DR. MORRY: I think you just summed it up very well. Those are the factors that we can look at that might account for the difference in the results. But, you know, when talking about the higher dose in the Senoh study, keep in mind that they did find statistically significant increases at the same -- at the lower doses, at 400 and below, which didn't show up in the Malley study. So it can't be explained totally by just going to the higher dose.

COMMITTEE MEMBER LANDOLPH: No. But also the fact that you've got a trend, which was statistically significant in a dose response in the Senoh studies makes me unable to throw those studies away. Plus, the fact that you've got them in males and females of both mice and rats. That's a composite. It's a lot of data. Do you agree with that?

DR. MORRY: Yeah. You know, they're four very positive studies.

COMMITTEE MEMBER LANDOLPH: Yeah. Thank you.

CHAIRPERSON MACK: Thank you.

Sol, do you have anything?

COMMITTEE MEMBER HAMBURG: Yeah. One question for the staff.

Is there any way to reconcile in the Senoh study that the maximal tolerated dose would have been exceeded because of the significant weight loss found in the mice, as well as in the rats, and say that the 800 parts per million was -- exceeded the maximal tolerated dose?

DR. MORRY: I think there's a question about the maximum tolerated dose with regard to the female mice, because they experienced more toxicity -- liver toxicity than the male mice or the rats. So I think that's a question for the female mice. But I don't think that's a problem for the other animals.

COMMITTEE MEMBER HAMBURG: Despite the fact that there was a significant weight loss in all the groups, I believe, at the end of the study which was beyond 10 percent?

DR. MORRY: But there wasn't a decrease in survival.

COMMITTEE MEMBER HAMBURG: No, there was not. But one of the criteria, as stated by DuPont, is a significant weight loss. And I think Senoh dismisses

that, but I want to know what your feelings are about that.

DR. MORRY: I think Senoh dismisses it for the other animals, but for the female mice they acknowledge that that might -- that high dose might exceed the maximum tolerated dose for the female mice.

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: If I could add. The question of whether the dose is adequate or the dose is excessive has been addressed by the U.S. EPA in their 2005 cancer guidelines. And they suggest that, to make sure there's been adequate dosing, you do want to see some weight loss. They also say that excessive weight loss may be an indication of excessive dosing. But I think that "may" is an important qualification.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: Just a comment. Maybe you can clarify this. But I went to the EPA cancer guidelines and read this section. And DuPont had excerpted part of it, but they had skipped a sentence. And the sentence basically says, if the test agent does not appear to cause any specific target organ toxicity or perturbation physiological function, an adequate high dose can be specified in terms of a percentage reduction of body weight gain over the life span of the animals.

In this case, it appears that the test agent does cause a specific target, organ effect. So there's much more flexibility, I think, in this percent of body weight gain. It's actually reduction in body weight gain rather than loss.

So I'm not sure that 10 percent figure should be held as sort of a standard in this case.

CHAIRPERSON MACK: Okay. If there are no more questions, we'll go to the "comments" section. And I understand we have a tag team presentation, one from DuPont and the other from -- Stan Landfair and Linda Malley.

I presume you're Stan.

MR. LANDFAIR: Yeah, thank you, Dr. Mack. Let us get our act together here. Just a second.

Do you have our PowerPoints available to you on your screen?

(Thereupon an overhead presentation was Presented as follows.)

MR. LANDFAIR: Thank you, Dr. Mack; thank you, Joan; and thank you to the remaining members of the Committee.

I truly thank you for the opportunity to be here. And we share the post-election glow. And we have brought with you -- to talk to you, two DuPont personnel that I

think you'll want to talk to very much. And they had the opportunity to see the country turn from red to blue as they moved from east to west yesterday.

(Laughter.)

MR. LANDFAIR: My name is Stanley Landfair. I'm from the Law Firm of McKenna, Long & Aldridge. I'm pleased to represent DuPont.

Whenever I participate in these proceedings, I'm always very mindful of the fact that I'm a lawyer, not a toxicologist, and this is principally a scientific judgment to be made.

What I would like to contribute, before introducing our participants, by focusing just for a minute on the criteria that govern your decision.

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MR. LANDFAIR: And the standard is written into the statute. We define a statute as known to cause cancer if in the opinion of the State's qualified experts -- and that's clearly you -- only if it has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

Now, I want to emphasize that, because sometimes that gets lost in the discussion.

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MR. LANDFAIR: And we're here not just to discuss

some data, but to balance data and to see what the weight of the evidence shows in total. And that's why the regulations actually impose upon you the same duty that's written right into the statute, is to weigh the data and see if, at the end of the day, this chemical has been clearly shown, through scientific data, to show cancer.

And we're going to ask you to balance the weight of the evidence and to give a fair hearing to all of the evidence.

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MR. LANDFAIR: Now, it's obvious that the reason I have to make this introduction is because we have a disagreement. It's unfortunate that this is the first exchange of information between DuPont, who is both the principal manufacturer of this chemical in the United States and the principal repository of the scientific data concerning this substance, and the agency. And unfortunately, that is DuPont's fault. DuPont did not -- was not aware of the data call-in notice a year ago and did not respond with data. Our first submission to the panel -- to the agency is the submission we've made to the panel. And it sounds like from your questions you've had the opportunity to see it. But I just would like to make sure you all have received our submission, including, in particular, a letter of approximately 18 pages on my

stationary.

Well, thank you.

It's very important that we go through that data and that we have this opportunity to address this collaboratively with you as well as with the agency, in a way that we feel that if we had had this discussion a long time ago, we would not be having this discussion now.

But we have brought before you the principal author of the Malley study. Obviously, we've got a perceived conflict between the results of the Malley study and the Senoh study. The Malley study was commissioned by the NTP. NTP asked DuPont to conduct it and to conduct it according to NTP guidelines. And it was the basis of the IARC conclusion, intending to show that DMF is not carcinogenic. And we would like the same opportunity -- or the full opportunity to explain why we don't believe the Senoh study is an adequate basis for changing that conclusion.

At the same time, we -- or following that, we'd also like to introduce Dr. Morel Symons, who's the chief epidemiologist for DuPont, who's prepared to address with you, in considerable detail, all of the findings of the Chen study, which again was a DuPont study.

And they are not new to this question. They're authorities in this area. And we hope that you will be

just as probing with them in their questions to you as you were to the staff, because they have quite a bit of information to convey to you. And we're quite confident that, at the end of the day, they can resolve any concerns that you might have.

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DR. MALLEY: I appreciate very much the opportunity to present our position to the distinguished members of this Committee. And I'm going to be presenting the discussion of the animal studies today.

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DR. MALLEY: And I just want to mention that we've studied DMF toxicity for many years. We have a very robust toxicity database and very complete with regard to both repeated dose toxicity, developmental, reproduction, metabolism, pharmacokinetics, genotox, and the epidemiology study.

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DR. MALLEY: The two studies in question are the Malley study and the Senoh study. And you've already noticed that they've both used the inhalation route of exposure, both rats and mice, both identified the liver as the target organ. But they both ended -- but they ended up with different results at purportedly overlapping exposure concentrations. And I can explain to you today

why we ended up with those different results.

And we feel that it's the differences in the chamber atmosphere generation technique that Senoh used that has resulted in a much higher systemic dose in that study. We also believe that the MTD was exceeded in the Senoh study, due to the higher concentrations and aerosol deposition on the animals.

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DR. MALLEY: Okay. So I'm sure you're very familiar with the concept of maximum tolerated dose. But I just want to take a second to review with you the EPA and OECD guidelines that specify what it looks like when the maximum tolerated dose has been exceeded.

First, as was mentioned, a significant decrease in body weight gain. They also mention significant changes in clinical chemistry; saturation of detoxification and clearance mechanisms; and marked changes in body weight, tissue morphology, and histopathology.

And it's important to pay attention to the maximum tolerated dose. Because when you saturate the absorption and detoxification pathways, it can result in tumor formation that's secondary to cytotoxicity.

And cancer that is observed only when you have exceeded the MTD does not clearly show that the test

substance is a carcinogen.

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DR. MALLEY: Okay. You've already seen the Senoh data, so I'm not going to go through the tumor incidence again. But I do want to call your attention to some other additional parameters that are indicative of saturation of the metabolic pathway and exceedance of the maximum tolerated dose.

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DR. MALLEY: You'll note on this slide that there's a substantial decrease in body weight in the male mice and the female mice, which you'll see on the next slide, at all exposure concentrations in the Senoh study. You'll also notice that the relative liver weight is greatly increased at all exposure concentrations.

And Senoh presented the serum chemistry enzymes. He measured three of them. I've only presented an example, one here. But you can see that there's actually a nonlinear change in the serum enzyme response. Hepatocellular single-cell necrosis also has a nonlinear increase incidence, as does the centrilobular nuclear atypia has a nonlinear increase in incidence. And, of course, you can see the nonlinear increase in the incidence of the tumors as well.

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DR. MALLEY: You see the very similar pattern in the female mice, so I'm not going to belabor each and every row.

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DR. MALLEY: But this nonlinear response in the serum enzyme activity, the tumor incidence, and the non-neoplastic and pre-neoplastic changes indicate that there has been a severe impact on the liver function and that the maximum tolerated dose was exceeded at 200 parts per million and above.

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DR. MALLEY: Looking now at the Senoh rat study. We see a similar pattern of effects, although not as severe. Increase in relative liver weight. Increase in serum enzyme chemistry. Increase in pre-neoplastic spongiosis hepatis. This occurs only in the male rats, because it's a male-specific lesion. And increase in hepatocellular adenomas and carcinomas, as previously mentioned.

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DR. MALLEY: In the female mice, it's a very -- or sorry -- female rats it's a similar pattern. In this case, the female rats responded with an increase with the centrilobular necrosis.

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DR. MALLEY: Also, notably in this study, the survival of the 800 part per million rats was significantly impacted, which --

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DR. MALLEY: -- again is another indicator of exceeding the MTD.

So we have increased mortality. We have substantially decreased body weight at 400 and 800 parts per million. We have increased hepatic tumors at 400 parts per million and above. We have dose-related increases in hepatic enzyme activity in males and females at 200 parts per million and above. And all of these parameters taken together indicate that there is a severe impact on the liver function, which demonstrates that the maximum tolerated dose was indeed exceeded at 400 parts per million and above.

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DR. MALLEY: Okay. As Stan mentioned to you, the NTP conducted the preliminary 13-week studies in rats and mice. And they approached DuPont to conduct the long-term studies, because we had the facilities available that they didn't have. The NTP had originally wanted to co-expose the rats and the mice at the same time in the same chambers at the same exposure concentrations. And they didn't have chambers large enough to do that. And we had

the facility to do that, so we undertook this for them.

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DR. MALLEY: So, we used exposure concentrations of 25, 100, and 400 parts per million. And as you already have seen from the data, we did not see any increase in tumor incidence, neither adenomas or hepatocellular carcinomas. We did, however, see an increase in relative liver weight at 100 and 400 parts per million. And we saw an increase in the hepatocellular single-cell necrosis at 25 parts per million and above.

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DR. MALLEY: And we saw the same pattern among the female mice as well.

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DR. MALLEY: So, based on the criteria of achieving an MTD but not exceeding an MTD, our study shows that we did, in fact, achieve an MTD without exceeding the MTD, at which there was no increase in the neoplastic lesions.

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DR. MALLEY: Let's look now at the rat study. There was a significant decrease in body weight at 400 parts per million in the males and 100 and 400 in the females, increased liver weight at 400 parts per million, increase in serum sorbitol dehydrogenase activity. This

is an enzyme that Senoh did not measure. It turns out that it's more sensitive than the enzymes that he did measure. We measured also the aspartate aminotransferase, alanine aminotransferase, lactose dehydrogenase. And we didn't see any increase in those enzymes. The only enzyme that we had an increase in, and it was a very minimal increase, was the sorbitol dehydrogenase activity.

We saw an increase in the hepatocellular single-cell necrosis at 400 parts per million. And no increase in the incidence of adenomas or carcinomas.

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DR. MALLEY: And you can see here the data for the female rats.

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DR. MALLEY: To summarize, we saw a decreased body weight, minimally increased serum sorbitol dehydrogenase activity, increase incidences of non-neoplastic microscopic changes at 400 parts per million and above.

All of these collectively taken together indicate that we achieved the MTD, but did not exceed the MTD. And we did not increase any neoplastic lesions.

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DR. MALLEY: All right. You've already seen that there's similarities between the studies. But in order to

understand what happened and why there's such a difference between our study results and the Senoh study results, we have to do a careful side-by-side comparison of the studies and the techniques that they used and that the DuPont team used.

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DR. MALLEY: First of all, the obvious thing is is the exposure duration for the mice is 18 months. This was specifically guideline driven by the EPA guideline as requested by NTP.

The method of atmosphere generation, I'm going to go into great detail about that on the next slide. And it is very important to the discussion. And the dose level selection for the two studies is important. And the differences in the rodent strains is going to be important.

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DR. MALLEY: Okay. So let's go into the method of atmosphere generation.

First, I'd like to point out to you that the vapor pressure of DMF is low at room temperature. It's only 2.6 millimeters of mercury. This means that it's very hard to generate this vapor without generating -- co-generating an aerosol. And it has a propensity to condense not only upon itself but on cold surfaces.

So in order to use these large exposure chambers that we had, the nine cubic meter exposure chambers, we had to develop a method to ensure that we had only vapor present in the chamber. And the reason why you want to have only vapor is because if you end up with an aerosol in the exposure atmosphere, that aerosol is going to deposit on the fur of the animals and on the exposed skin surface area of the animal.

And in the case of DMF, which is very extensively absorbed by dermal exposure, this makes a significant difference.

So it was very important to prevent formation of aerosol in the exposure chamber.

So to do this, we had to use heated air that we pumped into a J tube, which you have a diagram of on your slides. The DMF was dripped down -- literally dripped down the sides of the J tube and the heated air pumped up through the J tube. This formed the vapor that was desired. But we also had to keep the entire apparatus heated while we did this. Otherwise, we found through our experience that we would end up with condensation occurring as the vapor entered the chamber. And we had to ensure ourselves that we didn't have an aerosol in the chamber.

We also -- one of the other things we did was to

keep the airflow in the chamber very high. We had 1,100 liters per minute of air flowing through the chambers. And I don't know if you have any perspective for that, but it was -- that's a very high airflow. It does meet the OECD guidelines for 12 air changes per hour. And this is important, because if you have less than appropriate airflow in the chamber, you can get a buildup of ammonia from the excreta of the animals. So you'd be co-exposing the animals to not only the test material of choice, but also to the high concentrations of ammonia.

Okay. So how did we assure ourselves that, we, DuPont, how did we assure ourselves that we did not have an aerosol in the chamber? We used a cascade impacter to demonstrate that we did not have any detectable aerosol in the exposure concentration. Because GC chromatography, which we also used, will not distinguish between an aerosol or a vapor. It will only give you total amount in the air. So, we were assured that our generation technique did not result in any aerosol formation.

On the other hand, when I closely examined the Senoh paper, they wrote in their paper that -- in this first bullet, under the Senoh, that they sprayed liquid DMF into the air space of the solvent generation chamber.

Now, I don't have a picture of their solvent generation chamber, but I do know from working with DMF

that if you spray the liquid DMF into the chamber as an aerosol, if you start out as an aerosol, and you have a low flow through the chamber, which they did, it's going to remain as an aerosol. It is not going to vaporize to a substantial extent. So that you will have a vapor aerosol phase in the chamber.

Now, Senoh reports that he used air changes -- six air changes per hour. He didn't report the actual airflow through the chamber.

But six air changes per hour is not adequate to prevent co-exposure to ammonia. And he apparently also co-exposed rats and mice in the chamber, 50 of each sex. So we're talking about 100 rats and 100 mice in the chamber together for six hours. So the ammonia concentrations are going to get pretty high, unless you do something to make sure that you clear them out.

So his -- and he only used GC to sample his exposure chamber concentrations, which would again not have detected the presence of the aerosol in the chamber.

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DR. MALLEY: So, we believe that the delivered dose in the Senoh study is most likely much greater than the measured air concentration, because these animals would have had the aerosol deposit on their fur and the animals would subsequently groom themselves and obtain an

oral and a dermal exposure from the aerosol on their fur.

And we know from other studies that DMF has a high dermal absorption rate. So they would not only have oral exposure from the grooming; they would have dermal exposure from the high dermal absorption rate.

Now, the nonlinear tumor response and the nonlinear serum chemistry responses observed is very consistent with this pattern that they exceeded -- of a very high exposure concentration, higher than what they reported in their paper.

So, therefore, we can only conclude that the dose to the animals in the Senoh study can really not be determined from their study, because we don't know the actual concentration that the animals received.

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DR. MALLEY: Okay. So that's the vapor generation part of the problem. Now, I want to switch gears and talk about their dose selection, which also leads to part of the problem of why we ended up with such differences between the studies.

And various governmental agencies give us guidance on how to select doses for oncogenicity studies. And they say that we need to consider nonlinearities in the dose response. We need to take into consideration the pharmacokinetics. And we need to produce -- we need to

expose the animals to a dose that produces some toxic effects without unduly affecting the whole physiology of the animals.

And they also further provide criteria by which we can decide whether a dose has been exceeded. And they specify 10 percent reduction in body weight gain, significant changes in hematology or clinical chemistry parameters, saturation of the absorption or detoxification pathways, and marked changes in organ weight an histopathology.

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DR. MALLEY: In the Senoh study, we had all of these. We had excessive mortality in the female rats. We had greater than 20 percent change in body weight in both rats and mice. And we had a flat dose response for tumor incidence and hepatic enzyme activity in the mice. And all of these indicate that not only was the metabolic pathway saturated, but also the maximum tolerated dose was exceeded.

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DR. MALLEY: Okay. You've already seen the DMF metabolism, so I won't go through this slide. I just want to point out that we believe that the metabolism is saturated from the conversion of DMF to the DMF hydroxylated metabolite.

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DR. MALLEY: And we have some data to suggest this. This was conducted by my colleague at DuPont, Steve Hundley. And he conducted -- he conducted some studies prior to the onset of the or the start of the oncogenicity studies, so that we could have an understanding of the pharmacokinetics and select appropriate doses.

For this we used rats and mice. We used single and repeat exposures. The single exposure was a single six-hour exposure. The repeat exposure was ten consecutive exposures. And at the end of these exposures, we had a 24-hour blood collection period in which we measured DMF and the various metabolites.

The exposure concentrations were 250 and 500 parts per million. And what I have shown here on the slide is the results of the measurement of the parent compound, DMF, in the plasma. I'm not going to show you the other metabolites at this point in time.

But you will notice that I've expressed the data as micromole per hour per part per million. What this does is allow us to calculate a ratio of the result from the 500 part per million to the 200 part per million. And if that ratio is 1, that's an indication that the pathway -- the detoxification or clearance pathway is not saturated. If the ratio is greater than 1, that is an

indication that the pathway is saturated.

And so if you notice on the column entitled "Ratio," for a single exposure, the pathway is saturated in both rats and mice, and substantially saturated in mice to the extent that it really indicates the metabolism is saturated below 250 parts per million concentration.

Repeat exposure induced the enzyme activity in the liver. You can see that, because the ratio decreased. But for rats, it was 1.6, indicating that there is still -- the saturation is still beginning to occur. And for mice you can see that the pathway is completely saturated again below 250 parts per million.

Okay. So it seems to have frozen up.

CHAIRPERSON MACK: Metabolism is obviously saturated there.

(Laughter.)

DR. MALLEY: Yes, it's completely saturated.

Well, in any case, I was going to talk about the strain differences because that contributes. And I don't necessarily need the slide up here to talk you through the strain difference situation. We used the CD -- here we go.

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DR. MALLEY: We used the CD mouse for our study and Senoh used the BDF1 mouse for their study.

The CD-1 mouse, you'll see in its nomenclature here the ICR designation. That designation indicates that this mouse is genetically the same. Whether you buy the mice in Pittsburgh or whether you buy the mice in India or you buy the mice in Korea, they are genetically the same worldwide. They are the gold standard for conducting oncogenicity studies.

The BDF1 is a hybrid mouse of the C57BL/6 and DBA strains. This is an uncommon strain. In fact, I tried to find information on the longevity of this strain and the baseline tumor incidence of this strain, and even Charles River, who supplied the mice, did not have a baseline set of tumor -- or baseline tumor profile for these mice.

Typically, hybrid mice like this are used for -- and I don't -- specific animal models of disease or used for specific therapeutic models that people want to test. They're not typically used in hazard identification studies, such as the one that we undertook. And, in fact, the OECD guidelines specify that you need to use commonly used laboratory strains in your studies.

So because this strain is uncertain with regard to its response to both noncarcinogens and carcinogens, the applicability of this strain for risk assessment is really not clear.

Okay. You're going to have to...

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DR. MALLEY: Okay. Well, I was going to talk about genotoxicity after this anyway.

As was presented, DMF has been well studied with regard to genotoxicity. And, in fact, there are over 66 genotoxicity studies, both in vitro and in vivo. They've tested bacteria, yeast, insects, mammalian derived cell lines, and in vivo.

It was negative in approximately 20 in vivo, mammalian, and insect assays. And it was positive in only 6 in vitro assays.

Now, this was extensively reviewed, as was brought out by the IARC Committee in 1999. And IARC concluded that it was -- the negative -- the results have been consistently negative in well controlled studies. The six positive in vitro studies all had issues with them that made them not -- to be considered not well controlled.

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DR. MALLEY: So, to summarize. DMF only induces hepatic tumors in situations where the metabolism is saturated and there is evidence of severe hepatocellular cytotoxicity. We've already demonstrated and mentioned that the liver is the target organ. And we've presented data that it's not genotoxic.

It was brought up about two human studies in which there was genotoxicity information suggestive that DMF exposure caused an increase in mutations. But there was -- it was confounded by a co-exposure to other chemicals.

There was one study in human workers that had an increase in chromosomal aberrations. The problem with this study -- I did review this study. The problem with it is that it did not take into account the smoking history or the alcohol consumption history of these people. And it was a very small, extremely small sample size.

So to conclude, based on that piece of evidence alone, that DMF is genotoxic or weakly genotoxic is not an appropriate conclusion.

Are there any questions, at this point, on the animal data before I turn the podium over to my colleague, Morel Symons?

COMMITTEE MEMBER LANDOLPH: Hi. Thank you very much for your presentation. It's nice to have you here.

I had a couple of questions. First one is with regard to strains. Now, the NTP usually has used a B6C3F1 mice. And how does your strain differ from that?

DR. MALLEY: They're very similar in their tumor response. The NTP used the B6C3F1 strain for their

13-week study. And, in fact, the B6C3F1 was used for the metabolism studies that I presented to you that were conducted by Hundley. So the results between the studies of the different -- the B6C3F1 strain, I expect those results to be similar to the CD-1 mouse strain.

COMMITTEE MEMBER LANDOLPH: And is there a reason you chose to use CD-1 rather than B6C3F1?

DR. MALLEY: It was just based on our own animal husbandry. We have great historical control data for the CD-1 mice and we didn't have as much on the B6C3, and so we felt that we should use the one where we had the better historical control database.

COMMITTEE MEMBER LANDOLPH: Thank you.

And then I had a question on your male mice studies. I was noticing going down the table that there is a very high frequency incidence of hepatocellular adenomas in the male mice, 13 out of 60 in the untreated control group. Is that unusual according to your historical controls?

DR. MALLEY: No, that was within our historical control range.

COMMITTEE MEMBER LANDOLPH: Okay. And then the second question, there seems to be a big difference between the male and the female mice, because the female mice get zero out of 63 hepatocellular adenomas in the

controls. Is that also consistent with your history? And is it -- you just think it's a sex hormone difference or something causing that?

DR. MALLEY: Yes, that's consistent with our historical control data. And, yes, there does appear to be a sex difference. But if you notice, throughout the data I presented to you, there are various sex differences both in the rats and the mice in their response to DMF. So that's not unusual.

COMMITTEE MEMBER LANDOLPH: And then in your female mice studies, the hepatocellular carcinomas go -- they're clearly negative. But in the males, the hepatocellular carcinomas go zero out of 60, 1 out of 62, 4 out of 60, 2 out of 59. Did you do statistical analysis of that for the trend test?

DR. MALLEY: Yes. And it's not significant.

COMMITTEE MEMBER LANDOLPH: But it is an increase over the background for hepatocellular carcinomas?

DR. MALLEY: Right. But the background, you have to understand that that's the -- just the control. It's not increased over our historical control range. And an increase of 1 or 2 is biologically insignificant.

COMMITTEE MEMBER LANDOLPH: Thank you.

CHAIRPERSON MACK: Sol, do you have anything?

COMMITTEE MEMBER HAMBURG: Not right now.

COMMITTEE MEMBER WU: I just am curious. Actually, when you look at the mice Senoh paper and yours, you know, forgetting about over 400 ppm, if you just look at the lower doses, really the difference is really between the 0 ppm group and the next group. It's really the baseline group that really differ in the two studies. So I'm -- as an example, in your study, the relative liver weight -- and they were pretty consistent in both male and female mice. And in the Senoh studies really the zero group, the baseline group is really different.

So I'm wondering -- I just want to see if you have any insights as to what -- it has nothing to do with even, you know, what dose are they using. It's really the baseline group that differs.

DR. MALLEY: The relative liver weight that you see there, that's not the absolute liver weight. That's the liver weight divided by the body weight of the animal. So you can't compare the relative liver weight of the mice in the Senoh study directly to the mice in the Malley study, because the body weights are different between the animals, between the different strains. So it's a function of the body weight.

Did I answer your question? I'm not sure I did.

COMMITTEE MEMBER WU: I'll think about it.

DR. MALLEY: Pardon?

COMMITTEE MEMBER WU: I'll think about your answer.

DR. MALLEY: Okay.

CHAIRPERSON MACK: Sol.

COMMITTEE MEMBER HAMBURG: Do you have any data for 24 months rather than 18 months at all that you could speak to?

DR. MALLEY: In the B6C3F1?

COMMITTEE MEMBER HAMBURG: In your study.

DR. MALLEY: Oh, in the CD?

COMMITTEE MEMBER HAMBURG: Did you extended any further than --

DR. MALLEY: No, we did not extend it. We followed the EPA guideline. And we were working in collaboration with the NTP, and that was their specification to end the study at 18 months.

The 18 months is a standard regulatory end of study for mice, because of their longevity and age-related diseases that they develop. If you're registering pesticides or other chemicals, you either do it -- you do an 18-month mouse study and a 2-year rat study. So the 18-month is typical of what you're supposed to do for any compound, whether it's pesticides or chemicals.

COMMITTEE MEMBER HAMBURG: Okay. And a follow-up question.

Was there any necropsies done on animals earlier than 18 months at all to look for liver toxicity earlier?

DR. MALLEY: Yes. We did -- we had an ancillary group of animals in -- both ancillary group of mice and rats, in which we measured the cell proliferation activity in these animals. I didn't present this data because it was negative. It was not interesting. But we did interim necropsies at, I think it was, 3 months, 6 months and 12 months. And not only did we not see any increase in cell proliferation activity in either the rats or the mice; we didn't see any liver pathology either.

COMMITTEE MEMBER HAMBURG: Okay. And the reason you max'd out at 400 plus per million rather than 800?

DR. MALLEY: Is because of the saturation of metabolism.

COMMITTEE MEMBER HAMBURG: Thank you.

CHAIRPERSON MACK: David.

COMMITTEE MEMBER EASTMOND: I have a number of questions for you.

Let me just start with the first one. I found the Malley study a little unusual in that rather than talking about number of tumors per animal, it's number of tumors per tissue examined. And so it was virtually -- it was very difficult to figure out how many animals were actually examined. Is that -- I mean, that seems very

unusual to me. I'm assuming that it was one tissue per animal, but it's very unusual they would present it that way.

DR. MALLEY: On the slides or the presentation, I have shown the data as per animal.

COMMITTEE MEMBER EASTMOND: Okay. Because in the paper it's per tissue examined.

DR. MALLEY: Actually, I think it's per animal. It may be written as -- it may be inferred as per tissue, but it is per animal.

COMMITTEE MEMBER EASTMOND: Okay. Footnote B says per tissue examined.

The other question I have really comes down to this issue about maximum tolerated dose. And I'm trying to follow. You have a couple of arguments here.

One is that there's extensive -- there's non-neoplastic toxicity seen in the target organ. But if I look at many other carcinogens, that's very common. For example, with benzene you see myelotoxicity initially, and eventually you'll see leukemia. If you look at hormones, you'll see cell proliferation in a target organ. Eventually, you'll see cancer. So the fact that you have toxicity occurring in a target organ for me doesn't negate the value of that study.

And I mean -- I don't know. That's the one

issue, and I don't know if you want to respond to it.

The second one -- there's actually several of them. I don't quite understand the saturation argument, because I could make the same argument with benzene. Benzene saturates the metabolism in humans. It saturates somewhere between 1 part per million. And yet humans were exposed to much higher concentration of that, and that's where the leukemias are seen.

So if you say, well -- if you were establishing animal studies, you say, well, we would discount any studies above 1 part per million, because it's above saturation; well, then you may never have picked up that benzene causes leukemia.

So can you elaborate a little more on that, on the saturation issue, why that is particularly relevant in this case?

DR. MALLEY: It's relevant because you've altered the physiology of the animal and their ability to handle the test material and other things that they would be exposed to in their environment. And once you've altered the physiology of the animal, the response is not as relevant as if you have an animal that is functioning normally -- in its normal physiological state.

Yes, you can see that benzene or, for example -- perhaps let's use saccharin as an example. There's a

two-year rat study where animals were dosed with high doses of saccharin, which exceeded the maximum tolerated dose, and you ended up with bladder tumors.

There's lots of these cases where you have exceeded a maximum tolerated dose and you ended up with a tissue response that is not relevant to the normal use of that material.

So, you know, a normal use is not going -- for a normal use with DMF, for example, is prescribed to be capped at 10 parts per million. That's the TLV, that's the DuPont acceptable exposure limit, it's the MAK, it's all -- a number of countries have their own regulatory guidelines capping the exposure concentration at 10.

And the guidelines for setting doses say that you're supposed to use realistic exposure concentrations. So if your known exposure is going to be 10, and you're exposing them to 800 parts per million and you get tumors, that's not relevant to what's happening at 10. You understand the --

COMMITTEE MEMBER EASTMOND: Oh, yeah, I certainly understand. This is a classic issue with design of animal cancer studies. The animal cancer studies use small numbers of animals. And so, therefore, you use higher doses because you're trying to extrapolate to very, very large numbers of individuals in the populations you

expose.

So I mean artificially lowering the doses just because you have a TLV at 10 ppm or something is not commonly done for many different types of cancer studies, because you're working with small numbers of animals relative to the population when we exposed.

DR. MALLEY: But these animals were exposed up to 400 parts per million. And that was above the level of saturation in mice and approached the -- was close to the level of saturation in rats -- metabolic saturation. If we went higher, we would have altered the physiology of how these animals were able to respond to the test material and we would have altered the tumor profile. If we had gone higher, it would have changed the animal's ability to clear the test material from the body and ultimately the damage would accumulate.

COMMITTEE MEMBER EASTMOND: Then the Senoh studies, they saw increase in hepatocellular carcinomas at the 200 ppm concentration in the mice. So this is actually -- certainly hasn't exceeded your -- you know, what you said as far as the kinetic profile or where you believe saturation is occurring. So there's a significant increase even at the lowest tested dose.

DR. MALLEY: You have to keep in mind that the Senoh study, we don't really know that they got 200 parts

per million. They probably got a much higher dose. We just don't know what that dose is.

COMMITTEE MEMBER EASTMOND: I have one more.

The one other thing was when you went through some of these different agencies that have their maximum tolerated dose that, you know, you referred to, I spent several hours in the library yesterday looking at maximal tolerated dose in reviewing this and looking. And actually, you've kind of selectedly presented that information, both in your written document and your presentation. Because in the EPA cancer guidelines in the 2005, it says these may be used or they implied they may not be used, that it really is a judgment call based upon whether these different criteria are seen.

And, in fact, that doesn't come across in my mind. And the overheads say these are the sort of criteria -- well, it's left very much in disorder, the judgment call; these may be of interest, they may not be. As I mentioned before, there's a specific sentence where you have target organ specific toxicity that decrease in body weight gain doesn't appear to be as sort of a critical threshold. At least that's in the guidelines as I read them.

DR. MALLEY: Yes. But you still had increases in non-neoplastic histopathological changes, indicating that

we did achieve an MTD in the Malley studies.

The issue of why we wouldn't use the doses that we used was 1) we didn't want to saturate the metabolism pathway, 2) we wanted to stay within the realm of the realistic exposure concentrations. And we didn't want to exceed the maximum tolerated dose, because once you have done that, the ability to interpret the results, it leads you to the exact situation that we're in now. We don't know how to interpret the Senoh results, because they exceeded the maximum tolerated dose. We don't really know what dose they received. And since they've exceeded it, it makes it very difficult to interpret their results and use them for risk assessment. And that's ultimately what we're conducting the study for, is for risk -- the purposes of risk assessment and understanding the risk to human beings who might be exposed.

We didn't do this study as a research type of study. We're doing it specifically to address risk assessment and knowing how best to protect people who might be exposed to the chemical.

COMMITTEE MEMBER EASTMOND: One last comment.

CHAIRPERSON MACK: I think we should probably move on, unless you've got something really --

COMMITTEE MEMBER EASTMOND: Just one last comment.

Well, it's not critical. That's fine.

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Dr. Mack, may I ask one question of clarification?

CHAIRPERSON MACK: Yes, Martha.

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Dr. Malley, in your presentation you discuss the method of generation of the DMF vapor by Senoh, et al. But I'm reading their paper on the toxicity due to 2-week and 13-week inhalation exposures.

DR. MALLEY: That's where you find that --

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: And if I read it correctly, in their "Method" section the 2-week exposure study they generated that DMF vapor air mixture by spraying liquid DMF into the airspace. However, they say in the 13-week exposure study the vapor air mixture was generated by bubbling clean air through the DMF liquid in the solvent reservoir, further diluting the vapor air mixture with clean air and supplied to the inhalation exposure chamber.

DR. MALLEY: The bubbling has the same action as spraying it. If you are bubbling the test material, you get an aerosol. If you spray the test material, you get an aerosol.

We worked with the DMF quite extensively during our method development phase for the oncogenicity study.

And this was a really tricky compound to generate a vapor without getting an aerosol in the chamber. Any time you bubble air through it, you're going to get an aerosol. I mean, we tried it and we got an aerosol. The only way we could get the air -- the vapor was to drip it down the sides of that J tube that I showed you while blowing air up through the J tube, because we tried a lot of different things during our method development that didn't work. And I remember, anecdotally, the technician called me on the telephone and said, "It's raining DMF in our chambers." And --

(Laughter.)

DR. MALLEY: -- so, you know, when they tell you that, you know, you have to pay close attention to aerosol versus vapor, because it really is a challenging material to generate.

CHAIRPERSON MACK: Dr. Malley, you certainly have gotten our attention. There are a couple more questions even now.

Anna.

COMMITTEE MEMBER WU: Okay. I'll make it very quick. And I hate to belabor this, but I'm still not understanding.

So are you saying that, in fact, the 200 ppm exposure level in the Senoh study is really not 200 ppm?

DR. MALLEY: Yes, that's exactly what I'm saying. It is not 200 parts per million.

COMMITTEE MEMBER WU: What --

DR. MALLEY: It's not 200 parts per million, because they have an aerosol in the chamber. The aerosol is a liquid droplet. And the liquid droplet will deposit on the fur of the animal. And the animals, once they're in the chamber, they're going to groom themselves to remove the deposited aerosol. So not only do you have the inhalation exposure; you have the oral exposure and you have the dermal absorption on the exposed surfaces of the animal, you know, the tail, the paws, the ears and that sort of thing. So you've got absorption by three routes: Oral, dermal and inhalation. So we really don't know what their dose was at any of those doses - 200 was probably not 200, 400 was probably not 400, 800 was probably not 800.

CHAIRPERSON MACK: Okay. Martin.

Well, I have one quick stupid question. And, that is, if the desire to avoid the aerosols is largely because you don't want any dermal absorption because it goes much more efficiently, why has nobody done a sequence of dermal absorption studies, and starting at a very low dose?

DR. MALLEY: We have dermal absorption studies.

I just -- it wasn't part of this data review, and so I didn't present those data. But we do have dermal absorption data for DMF. We have had an extensive amount of dermal absorption data.

CHAIRPERSON MACK: And they have not produced carcinogenic effects?

DR. MALLEY: We haven't tested it for -- in a 2-year study or in an 18-month study in mice. We do know that from a very old study that subcutaneous injection of DMF did not produce tumors, if that gives you an idea. It's not directly the same, but it's pretty close.

CHAIRPERSON MACK: Okay. I think now we need to hear from your colleagues.

DR. MALLEY: Thank you.

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DR. SYMONS: Thank you. It's a great opportunity to come speak to the Committee, and I appreciate it. I also appreciate the effort that Lindsey put into it and the consideration that she gave to the comments that we provided.

To reiterate, Stan's discussion at the beginning, it is unfortunate that our awareness of the document was not timely enough to be able to work together in this. But I'm hoping that we can use this as a way to do that in future cases if the need arise.

Really, I want to concentrate on the history of the epidemiology, noting that what we're looking at is three groups of studies. And Lindsey characterized those very well. But those three studies were all done over two decades ago. And there have been no subsequent epidemiologic analyses that we would consider to be a comparative analysis, either of the case control or cohort design. And one of the reasons for that is I don't believe that there's been much to follow up on.

However, when we look at these three studies and then group them, we have the initial cluster investigation in F4 aircraft repairmen conducted by Ducatman and colleagues. And, at that time, Dr. Ducatman was working in the military as an environmental health investigator.

The cluster report, and then subsequent extension to that into a case control study, and really what I would qualify as a comparative incidence analysis. It's not traditionally a cohort study in that it did not include a large group of workers; nor did it consider many of the other potential health endpoints that we would look at in a cohort study. It focused exclusively on testicular cancer. And that study is actually more of an industrial hygiene report conducted by NIOSH investigators who collaborated with work -- collaborated with researchers from New York State Department of Health, from Mount Sinai

School of Medicine, and also representatives from the workers' union who represented the leather tanner workers.

And then finally the cohort studies and case control studies done by DuPont over two decades ago, which I was not around for; but hopefully I can add some perspective on, because they are consistent with protocols that we've used since then.

But the central questions we want to address with the human data are: Is the review, reanalysis, and interpretation by OEHHA of the human data correct and how we would look at this through an epidemiologic perspective? And finally, do these human data support listing under Proposition 65?

So if we go to the first slide.

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DR. SYMONS: I've also characterized how these studies were conducted, again noting that for the cluster investigations and the leather workers, the focus very early on was on a single outcome, testicular cancer. And this is consistent again with how cluster investigations are done.

The Ducatman study in aircraft repairmen did look at seven cases. Among them was 1,300 white males who were at three repair facilities. Two of those facilities had a specific process used that involved a depotting solution

that contained DMF. One of those facilities did aircraft repair, but in a different manner.

But looking at Ducatman's original report, it's also notable that there was also simultaneous exposures to many other chemicals in this occupation -- aluminum, aluminum alloys, electroplated surface materials, cadmiums, as well as zinc-chromate-based primer paints. And none of these other chemicals were considered in the discussion.

The leather workers study, which was published, I think, within months of Dr. Ducatman's original paper, started with an observation by three workers who had testicular cancer at a leather tannery facility, specifically the Pan American Tannery in Fulton County, New York. And as is typical with many occupational studies, that's really how some of these situations come to our attention, workers experience a health outcome, discuss among themselves, and notice some similarities and bring it to the attention of people who then subsequently do the research.

But it's also very important to focus on that the research hypothesis that was generated for this study was motivated exclusively by the earlier report in the aircraft repairmen.

The case control and comparative incidence

studies that followed up on this were described in separate reports and in additional documents that we have provided in our packet and also that Lindsey had noted. But, again, one of the key aspects of this study is that, though the tannery reported historic use of DMF, there were never any levels measured and there were not -- there were no levels detected by NIOSH investigators when they did an industrial hygiene analysis of the Pan American Tannery.

And it's very important to establishing, again, that this study focused on whether or not leather work was associated with testicular cancer, not whether DMF itself had any association with the cancer. Because one of the key aspects of this, as we'll discuss, is that there are lots of other chemicals used in leather working that have a tremendous toxicity.

Finally, the DuPont studies were designed in order to assess both acrylonitrile and DMF in fiber production facilities. And that was the goal of our cohort studies, those have been published under separate papers detailing the acrylonitrile-exposed workers. In fact, I recently published an update of 25 years of follow-up on those acrylonitrile workers earlier this year.

But the case-control study done by Walrath and

colleagues was also a part of DuPont's ability to try to contribute to the science of DMF that was being published at that time.

So why don't we move on.

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DR. SYMONS: Looking at the cluster studies, the initial report by Dr. Ducatman really details a hypothesis. And, again, it's the great utility of cluster studies and that we use them to posit a hypothesis before we do more detailed analytic studies. And that hypothesis, as Dr. Ducatman notes himself, was really arrived at after eliminating other candidate risk factors for DMF. And some of those candidate risk factors involved family history, trauma, mumps, maternal exposure to diethylstilbestrol, or DES, but did not really consider the full suite of chemicals that these aircraft repairmen were exposed to. And Dr. Ducatman himself concluded that the investigation raised, but did not prove the hypothesis.

That was subsequently followed by the report by Levin and colleagues. A letter to the editor of the Lancet describing the clinical history of these three testicular cases at the Pan American Tannery. And they state in their letter -- and I've excerpted the quote here -- that DMF became the focus of concern in light of

the report by Ducatman, et al.

So we did have a cluster situation in this leather facility, but the researchers themselves posited the hypothesis only because they were aware of Ducatman's recent publication.

And, again, I'll go into the details of leather tannery and the workers' exposures. But it's important to realize that that DMF hypothesis was not an original part of the leather workers' investigation. It became informed by what we derived from the cluster report by Ducatman.

And one of the notes that I wanted to make here is in both of these case studies -- and I believe Dr. Mack had asked this question earlier -- what was the profile of testicular cancer in these clusters? And they both involved a mix of seminomas and embryonal cell carcinomas -- or embryonal cell cancers. And unfortunately, I don't have enough of a background to understand -- a medical background to understand if there's a distinction -- I believe you on the Committee probably have more of a medical familiarity with the distinctions of testicular cancer. But I did want to note that this is in a mix of testicular cancers in both of these studies.

And I would direct your attention to Table 1 in Dr. Ducatman's 1986 paper where he lists the diagnoses,

and then also the letter by Levin to the Lancet where he describes the case histories of the three cases and notes that there was a mix of these two testicular cancer types.

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DR. SYMONS: I don't really need to spend much time on the limitations of cluster studies, as they're well known.

Again, they are very useful for generating hypothesis. But they do not provide us with any comparative analysis and they don't document any direct DMF exposure for us to assess. And, again, both of these occupations involve a lot of other chemical exposures that were not considered.

But I did want to note the last bullet on this slide, which is, if we're talking about high exposures to DMF, we have a very good physiological signal of that, and it's acute symptoms that are consistent with increased DMF exposure usually in the order of greater than 10 parts per million. And those include dermal flushing, or reddening of the face. Alcohol intolerance is also reported by workers who have high exposures to DMF. And liver disease or acute liver damage is a consistent symptom reported by those who are overexposed to DMF. And none of these symptoms are documented in either the Ducatman or in the New York leather tannery worker studies. In fact, the

NIOSH report explicitly states that they did not detect an increase in any of these symptoms in the exposed workers.

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DR. SYMONS: So if we look at the extension of the leather workers' study, it's reported actually in three documents: The State of New York's Department of Health report, which subsequently became an abbreviated publication in the CDC's MMWR, with the lead author being Frumin.

And then a third study, which I would have to apologize again, I just became aware of this study last week -- and I do believe that we've provided a copy of it to you -- conducted by the New York State Department of Health. Specifically, the lead investigator is Elizabeth Marshall. And this study complements the case-control study and actually extends it beyond Fulton County, New York, to the neighboring Montgomery County, New York, and adds an additional nine cases of testicular cancer to the grouping. So what we're talking about in the Marshall study is 19 total cases of testicular cancer in both of those counties.

And we did provide a copy to you. And, as I said, unfortunately I did not become aware of this until after we had already filed our draft response. So it is new information. But I hope to show you some pertinent

details from it that may shed light on the follow-up in the leather tanner workers.

Again, it's been noted by Lindsey as well as in our response, but there is a lack of any exposure estimates to DMF. It was no longer used at the index facility at the time the study was done. And there were no historic samples documenting its presence.

And there was no assessment done for any of the other chemicals used in the leather tannery. In fact, the NIOSH study has an appendix that lists all the chemicals that were contained in the inventory of the Pan American Tannery. And you can see there are quite a number there. And these include some metals; principally, as Lindsey noted, lead-based dyes; some synthetic dyes, which contain benzidine and anilines; as well as glycol ethers. And glycol ethers are known testicular toxins. They've not been shown to be carcinogenic, but they do do extensive damage to the testes.

Next slide.

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DR. SYMONS: So when we look at this case-control study, and this was captured by Lindsey's review, there are two really strong biases that really impact our ability to derive an inference from the reported risk estimate. And those biases, in epidemiology we would

classify them as a selection bias; that is, that there's a different age distribution between the cases and controls in this study. Testicular cancer predominantly affects young males, between the ages of 20 and 35. That's been noted.

But in the case-control study, we will see that the controls are on the order an average of a decade older. And this leads to an information bias that was raised by one of the questions earlier, which is that the exposure classification for these workers relied on a full case history -- a full work history for the cases. But the most recent occupation, at the time of other cancer diagnosis for the controls, was the only work assignment noted.

So what we're looking at is a distinct bias in terms of cases had full work histories taken, including "ever work at leather tanneries?" Whereas, controls only had their work -- their occupational assignment at the time of their diagnosis. And given that the controls were on average older than the cases, they had probably had, first of all, a more extensive work history; but, second of all, may have left leather working as they got -- or leather tannery work as they got older.

And so the inference that we derived from odds ratio is biased, and we don't even know the direction of

that bias.

Since the exposures defined only as "ever working at a leather tannery" and does not comprise any DMF information whatsoever, the only inference we can describe from that risk estimate is whether or not leather work itself, with all of its attendant exposures, is associated with testicular cancer.

Next slide.

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DR. SYMONS: So this is the details as I was discussing in a potential selection bias.

This table captures both the cases as well as the controls with known occupation in the study and those controls who did not have an occupation listed on their cancer registry or death certificate forms. And you can see right away the average age for the cases is quite in line with what we see, and testicular cancer primarily affecting young males, the average age being almost 32 years; whereas the controls, who were selected because they developed another form of cancer, but were also white males, are for those with known occupation on average 47 years of age and for those without occupation were 41 years of age. And, you know, sometimes an average can kind of smooth out distributional differences.

But I've also used the New York State Department

of Health information to categorize these by 10-year groupings. And you can see that for the cases, the predominant number of them were below 39 years of age. Whereas for the controls, the predominant numbers were above 40 years of age. And this is a very distinct difference that's going to potentially bias the findings from this study.

And if we look at the findings from this study, the primary risk estimate is the odds ratio. And, again, interpreting this odds ratio, you must pay specific attention to the fact that what it indicates is that "ever working in a leather tannery facility" has a 5.8 times probability increase in developing testicular cancer. There is no explicit mention of DMF exposure in this. And again, as I've shown, leather work itself has a whole host of chemical exposures that go beyond just DMF.

And so this slide is straight from the New York State Department of Health study, and it shows you, in kind of the simplest fashion, that is, the 2-by-2 table that epidemiologists prefer, how the cases and controls were exposed to this "ever working in a leather facility" designation. And it also notes again that 29 controls were missing any notification of exposure.

I've actually taken the liberty to revise the results with just a very simple kind of adjustment, which

is: If we assume that those 29 controls had 50 percent exposure to leather work, which would be consistent with the case profile -- so rounding errors to dividing 29 by 2, I went with the, you know, kind of more liberal estimate of 15 exposed and 14 not exposed, breaking that group in half, and adding them to the table. And you can see that what this does is it attenuates the risk estimate closer towards a no-effect value of 1.0.

But, more importantly, because of the small number of cases in this study, the confidence interval begins to lose its significance. And this is really what we're talking about here. Due to the small number of cases in these studies, questions of statistical significance are our predominant concern. And the inability of this study to maintain statistical significance with this slight adjustment is telling to the potential effects that this bias may have on the odds ratio that was reported in the original study.

Next slide.

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DR. SYMONS: Now, turning our attention to the Pan American Tannery itself -- and this is documented well in the NIOSH report -- this study, as I said, it's difficult to describe the cohort study, because it's primarily focused on an industrial hygiene and medical

screening report of the 83 workers at this facility, including the three original cases of testicular cancer.

It reports, what we call, Standardized Incidence Ratio, an SIR. And I believe one of the Committee members noted earlier that it was excessively high at 40.5. But, again, note that it has a very wide confidence interval.

And, again, if we go into the details of this calculation, on its simplest level, an SIR is the number of observed cases divided by the number of expected cases. And so to arrive at an estimate of 40.5, what we're looking at is three observed cases divided by .07 expected cases for this small number of workers over this short time period of almost a decade; basically saying we did not expect to see any cases in this group. So the fact that we saw three is excessively high and does raise some of the questions that prompted the cluster investigation. But it's difficult to attribute this again exclusively to some kind of comparison of workers who were more or less exposed to DMF.

Interestingly -- and this is where the Marshall study becomes very relevant -- subsequent follow-up of this group and an additional expansion of the study to include both Fulton County, New York, and Montgomery County, New York, both of which host over 50 leather tanneries at this time period, in the late 1980s, looking

at rates for testicular cancer in these two counties from 1974 to 1985, Elizabeth Marshall with the New York State Department of Health reported that the expected rate for this population of white males in these two counties was 25.7 expected cases for this time period. And their registry only reported 19 observed cases in these two counties.

Now, again, it's worth noting that this is a population of the county itself. And though there is a lot of leather tannery facilities in this county, this is focusing on the larger population. But that 19 observed cases and 25.7 expected cases changes dramatically the inference that we derive from a statistic such as the SIR. And it includes, again, a lot more individuals than were at the indexed tannery facility.

Specifically, as I noted before, the NIOSH report focuses on industrial hygiene of the facility -- of the tannery as well as medical screening for other workers. And they were able to gain the participation of 51 additional workers at the facility out of the 80 total who were not affected by testicular cancer. And that medical screening found no evidence of high DMF exposure consistent with those symptoms that I named before, flush, abdominal pain, alcohol intolerance, or any acute liver disease.

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DR. SYMONS: So really the conclusion that Calavert and colleagues, who were assigned to the NIOSH at that time, derived from this was that based on these findings from the medical evaluation, it is unlikely that overexposure occurred to DMF at the tannery. And we defined overexposure as 10 parts per million or more.

Now we can go on.

So coming to those conclusions, we have two documented descriptions of the conclusions from the NIOSH investigators. First, is their published form, which again was a letter to the editor of the Lancet published in November 1990. And they state that their investigation confirmed an excess of testicular cancer at the tannery. Again, I think we would all accept the fact that three cases, when .07 were expected, is a tremendous increase. However, they conclude that this adds to concerns about the carcinogenicity of DMF, but these conclusions should be tempered by the lack of detailed information about exposure to DMF, as well as many of the other coexistent exposures to chemicals at the tannery.

Interestingly, in their NIOSH report filed ten months earlier, they stated in their summary that because of the large number of these chemicals, the changes in engineering controls, the changes in chemical inventory

over time, that identification of the agent responsible for the cancer cluster is impossible. So I think we have to accept these researchers' conclusions that they have a compelling finding of additional cases -- of excess cases, but that the ability to discern whether or not DMF contributed to this is an undertaking that cannot be done in this study.

Now, at this time, I'd like to turn your attention to the DuPont studies.

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DR. SYMONS: Again, it's worth noting that the DuPont studies were conducted over two decades ago. The motivation for the Chen cohort study was based on, as Lindsey noted, some simultaneous work that we were doing in an acrylonitrile exposed portion of this work force.

Basically, to be brief, the Camden, South Carolina, acrylic fiber factory plant that was the subject of the Chen study, and identified as Plant C in the Walrath study, produced Orlon fiber. Orlon fiber is made from acrylonitrile. DMF is a solvent that's used in preparing the acrylonitrile for spinning into the fiber. And of the 5,000 workers at this Camden, South Carolina, plant, a large proportion of them had documented exposure to DMF.

Only one case of testicular cancer was noted in

this cohort. And, again, the DuPont Cancer Registry tracks all DuPont active workers during their time with the company. And when we're talking about these occupational cohorts, historically speaking, in the 1950s, 1960s, 1970s, many of these workers spent their entire careers at DuPont from the age of 20 until the ages of 50, 60, whenever retirement occurred. So we do have very adequate tracking of them for many decades.

The main finding from this study was that there were 11 cases of buccal/pharynx cancer. And what was shown in the report was that there was no increasing risk of this cancer with increasing DMF exposure or increasing duration to DMF exposure. And, in fact, all 11 cases reported heavy smoking for greater than 20 years.

Now, a question was raised earlier by one of the Committee members as to whether smoking was documented for all of these workers. Unfortunately, it was not. These registry-based studies really rely on work history information and medical screening data that we collect on our work forces. Only in rare situations do we have individual contact with workers. And this is one of those cases where for those 11 workers who were affected with buccal/pharynx cancer, the investigators did do subsequent interviews with them and got a smoking history. But for the remaining members of the cohort, we have no data on

smoking or alcohol usage, so we can't adjust for it or do any comparative analyses.

Again, to be balanced it's also worth noting that this smoking-alcohol effect was not looked at in the other populations that we're discussing here.

You can go to the next.

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DR. SYMONS: So what this led us to was the Walrath study. And this is a very interesting case-control study. And, in fact, some people would say, "Why does it contain such a odd collection of cancers?" And really the rationale is because, as Lindsey noted, some of the findings of melanoma, prostate cancer, and, of course, DMF having a specific target organ of the liver, the investigators wanted to look at cases of cancer in those organs. The buccal/pharynx results were followed up. And then again the testicular cancer cases were added in direct response to the Ducatman and Levin publications.

Across these four facilities involved in the case-control study, which included over 8,500 employees, there were 11 cases of testicular cancer noted. And when we looked at these cases, 8 of them occurred at the plants with the lowest exposures to DMF. That would be Plant A, the production facility -- or, I'm sorry -- Plant A is the facility that produced DMF, and Plant D is one of the

three plants that used it in manufacturing. And Lindsey provided great details on those -- on the exposures at those four plants.

And of these 11 cases, only 3 had documented exposure to DMF. While for the match controls 6 of those 22 had documented exposure to DMF. And, very quickly, the odds ratio here is 1.0. Basically, the exposure potential among the cases and controls is exactly similar -- or the exposure probability.

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DR. SYMONS: I will kind of spare the details on this, because I was very appreciative to see that Lindsey did pay full attention to some of the revised statistics.

But I want to go to this next table, which shows some of the comparative statistics that we've provided in our documented filing.

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DR. SYMONS: And one thing that's very much worth noting is, not just the P-values, whether or not they were one-tailed or two-tailed, whether they're derived from a Poisson distribution or a chi-square distribution. But really in occupational epidemiology what we tend to look at is the confidence interval. And this, in effect, is inherently two-tailed.

The confidence interval is a much more

informative metric for judging the significance. Because, again P-values just tell us whether or not a result that we report is significantly different from what we would expect, and that significant difference could be either higher or lower. But a confidence interval gives us a good sense of not only the directionality of the estimate but how wide the interval itself is.

And, again, because of the small number of cases for these observed cancer outcomes, we have very wide confidence intervals. And that coincides with the inference that's derived from the Poisson P-value, which most people would say is not significant as the standard except a rate of .05. Again, the confidence interval information should complement the P-value information, such that a nonsignificant confidence interval, i.e., one that overlaps 1.0, would have a P-value greater than .05.

And this is really why it's important to focus on the use of these two-tailed confidence intervals, mainly because the investigators compare multiple outcomes. I mean, we're looking at dozens of different health outcomes and different cancer diagnoses. And so one of the results that one always has to pay attention to, in these large cohort studies, is multiple analysis tend to bring in significant results just because of the shear number of comparisons being made. Again, the very basis of the

P-value is that you're expected -- if you use a P-value of .05 as your guideline, then you're saying, "I will see significant results five times out of a hundred."

So this is one of the problem areas that we run into, which is why the confidence intervals give us more information in order to interpret, quote-unquote, supposed excesses.

One of the things that it's worth noting here again is because of the small numbers of cancers for some of these outcomes and the wide confidence intervals, it's very difficult to draw any interpretation as to whether or not a specific occupational exposure was contributing to these.

So I would be happy to answer further questions on statistics. But, you know, as I said, I think that Lindsey did a very good job of recapturing the statistical analyses.

CHAIRPERSON MACK: I think there are people who have questions for you. But the person who's taking the record and my bladder both would require a few minutes of respect.

DR. SYMONS: I have one last slide. How's that?

So, in conclusion, from the epidemiologic evidence, we agree with OEHHA that more definitive studies are needed. And the fact that none of these studies have

been done in the intervening two decades, I think it's very informative to the fact that there is a lack of confirmatory epidemiologic evidence since the original Ducatman hypothesis.

I had the pleasure of meeting with Dr. Ducatman about a month earlier, and I mentioned to him this opportunity to come and address one of his earlier studies. And he was very intrigued that it was being considered because he felt that there was not really anything published since his original discussion of this that would lead him to believe that it was a hypothesis worth pursuing. But, again, that's personal communication that I had with Dr. Ducatman.

But, to be fair, all of these studies were reviewed previously by the WHO and by IARC. And I put the conclusions that both of those institutions arrived at for you.

WHO in a risk assessment published in 2001 said it's unlikely that DMF is carcinogenic to humans, looking at these same studies.

And IARC, as was noted, said that there was inadequate evidence in humans for carcinogenicity of DMF specifically regarding testicular cancer.

And, again, these are the same studies we've been talking about.

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DR. SYMONS: So, finally, to wrap up, what we're saying -- and I appreciate again the opportunity to discuss this with you -- that the weight of the evidence does not support a designation that DMF is a carcinogen. There's no evidence that it is associated with testicular tumors in humans. And as Dr. Malley noted, very suspect evidence that it may -- that the Senoh study may have exceeded the maximum tolerated dose. So I don't believe that that study can be accepted to say that it clearly shows the carcinogenicity of the substance.

And so I thank you for your attention and your time. And I hope I finished in a timely enough fashion.

CHAIRPERSON MACK: Thank you.

Ten-minute break.

(Thereupon a recess was taken.)

DR. SYMONS: I hope I'm still up.

CHAIRPERSON MACK: Okay. Let's begin.

First, I think we need some legal advice.

Where's the lawyer? There she is.

CHIEF COUNSEL MONAHAN-CUMMINGS: I could do that after you have the questions for the --

CHAIRPERSON MACK: Want to wait till after this?

CHIEF COUNSEL MONAHAN-CUMMINGS: I just wanted to do it before you do your deliberations.

CHAIRPERSON MACK: Pardon me?

CHIEF COUNSEL MONAHAN-CUMMINGS: I just wanted to talk to you before you do your deliberations. So you can finish with the public comments first.

CHAIRPERSON MACK: Okay. We're now going to try and address questions to you. And we'll let Dr. Wu begin.

DR. SYMONS: I'll be happy to entertain them.

COMMITTEE MEMBER WU: Technology deficient.

I am -- I flipped my page and I can't find it.

This is actually just some background information from you, so I have a better understanding of how these studies are being done in terms of following up workers.

So as an example, in the Chen study they, you know, mentioned that there were close to 4,000 workers who were exposed to DMF. And then in the Walrath study, there were roughly 8,000 employees who were exposed.

So in terms of the cancer registry, as well as updating this type of study, how does -- what is the procedure? I mean, how do you actually track and follow up what kind of health outcomes, you know, when is something elevated, when is something not? If you can just give me a quick update, because I'm not familiar with how this is actually being done.

DR. SYMONS: Okay. I will try to be brief. Unfortunately, you know, I really like what I do, so I

might go into too much detail.

COMMITTEE MEMBER WU: That's fine.

DR. SYMONS: But really your question, Dr. Wu, hinges on the DuPont cancer and mortality registries. And both of these registries were started in the late 1950s by Dr. Sidney Pell, who created the DuPont epidemiology program.

And Dr. Pell was still with the program, and you'll see his name on the publications that you refer to, Dr. Chen's study and Dr. Walrath's study in the late 1980s.

And what the registry involves is it -- focus on the mortality registry, first of all, which is documented in Dr. Chen's other publication on the Camden, South Carolina, cohort but one that we haven't paid as much attention to.

A mortality registry. Any time a worker starts work with DuPont, we add them to our HR database. And so moving forward, at this date we have about 280,000 workers in our database that we track by Social Security number. And relying on the National Death Index, we're able to ascertain vital status and then subsequent cause of death for those workers who are no longer with us. And for a company as large as DuPont with the long history, that includes quite a large number of current and former

employees, especially among those employees who are now pensioned.

The companion piece of that registry is the Cancer Incidence Registry. And, again, it's worth noting the history of the company. In the 1950s, '60s, and '70s DuPont had an extensive medical division; and like many other companies at that time, provided medical care directly to its employees. So when there was an incident cancer diagnosis in an active employee, we were immediately aware of it, because in some cases it was DuPont physicians making the diagnosis.

That changed in the 1980s, similar to a lot of companies, when we went to external third-party medical benefits. And, in fact, DuPont provides health insurance to all of its workers.

And from the late 1980s until about the year 2000, we unfortunately lost our ability to track cancer incidence in workers who were no longer active employees at the time the cancer diagnosis was made because they got their care from other health providers and therefore we had no subsequent follow-up on the reports.

But for active workers who had to miss work and then come back, they undergo a medical screening and so we file a cancer report.

But, again, our active workers, as is common in

occupational epidemiology and is well noted under what's called the healthy worker effect, they tend to be healthier and younger, therefore have less cancer than older workers.

Since 2000, our inability to track cancer incidence has been supplemented by a third-party provider who basically takes our health insurance information and goes through it for any diagnoses that involve usage for cancer-related reasons, and then we're able to update our registry.

So one of the benefits that this registry gives us -- and we are able to track many thousands of cases of cancer diagnosed in DuPont employees -- is that we become aware of these. But it also suffers from some limitations due to these temporal trends that I noted to you.

And I'll leave off there. And any other specific questions about how the registry operates, I'll hope to fill in. I know you probably want to go in the direction of, then how does it lead to a design study?

COMMITTEE MEMBER WU: Well, I guess my interest is, you know, the whole question -- I mean, it is very curious when I read this report that, in fact, there was nothing published since this flurry of letters and reports in 1988, 1989. So the suggestion is that it is actually publication biased, that somehow -- because I would

imagine that this group of individuals would have been followed and whatever the results are, that there would have been some, you know, report. So I guess my question is: Did DuPont actually do any follow-up studies on this group of individuals who were exposed? Because essentially, given what you just mentioned, you could easily have done -- linked them up in terms of, let's say, finding out what are the mortality outcomes, you know.

So, I guess, that's sort of where I'm trying to get a better understanding of, given that this was something that was of interest and potentially very important, you know, what is the follow-up actions with this group of individuals who were exposed?

DR. SYMONS: Yeah. For the DMF-exposed cohort, we have not had any subsequent analytic follow-ups, though we have the capability to address some of the questions that you raise. But it's always a question again of resources.

We pursue this registry-based surveillance for signal detection. But we also use it to do detailed analytic studies. In fact, a relevant example that was brought up by Ms. Roth -- and I apologize earlier for being so familiar -- was the acrylonitrile worker study. That study I published earlier this year was an update of the sub -- I'm trying to think of the right word -- the

subgroup of workers who were exposed to acrylonitrile within both the Camden, South Carolina, plant and the Waynesburg, Virginia plant. And that study I published in May of 2008 in the Journal of Occupational and Environmental Medicine detailed an additional 25 years of follow-up of our acrylonitrile-exposed workers.

Acrylonitrile's not the subject of today's conversation, but that study involved again some of these workers who were simultaneously exposed to DMF. Unfortunately, because of the fact that these studies were done over two decades ago, many of the records, especially the computer-based records with exposure, are not accessible to us. They're either stored on data tapes or in storage facilities. And so we don't have a very quick and easy way to just call them up and rerun the analyses or to update the analyses. It would involve a concentrated effort with a lot of resources to be applied to further ascertainment of the cohort, data checking, data validity, as well as in this case, with studies that were conducted over two decades ago, probably the migration of those records to new computer platforms, because I believe they were done on kind of mainframe-based systems that were typically used in the late 1980s. And now we obviously have a lot more power just on desktop alone.

So, in that sense, the potential is there. But because of resources and because -- again, I think the conclusion that we drew is that there was nothing that indicated to us that DMF increased the likelihood of cancer in exposed workers, that's why those follow-ups have not been done.

CHAIRPERSON MACK: Okay. I have a couple very quickies.

DR. SYMONS: Yes, Dr. Mack.

CHAIRPERSON MACK: And they all deal with exposure, because I find the differences between these various observations to be fairly profound in respect to exposure.

We heard about the sailors who were basically slathering 80 percent DMF all over some materials and doing it all day for a long time. And while there may be other exposures that they had, that sounds like a pretty severe one. And there may be others as well.

Now, when it comes to the tannery workers, my understanding was the three cases that popped up that recognized their own likeness, and while they may have had some differences in the histology, the fact is all three -- all what, all seven of them were germ cell testicular tumors. In other words, that covers both seminomas and the others which you mentioned. And that means they had a

common source or origin at some point.

We were told that they slathered the material, and I presume that that included the chemical we're talking about, over the hides in some way with a paddle. Now, that, to me, doesn't sound like it's going to be a typical exposure of tannery workers generally. So that sounds like a very specific, probably much higher exposure. And it also sounds similar to the Navy people because we're talking about people who actually have a liquid that they are in pretty close contact with. And they had a dermal exposure.

But the likelihood of having aerosols, for example, is probably pretty big in both of those circumstances.

So I am suggesting that there may be big differences among the tannery workers and that there may well be a very small -- much smaller subgroup who had this kind of exposure. I know we don't know and there's nowhere we're going to find out.

Now, with respect to DuPont, can you describe to me, in a little more detail, the actual nature of the exposure that workers would have in the Orlon manufacturing process to this chemical. Because I can't imagine with industrial hygiene practices the way I presume they are at DuPont, that there's going to be a vat

of this stuff and the Orlon is being dripped in and out of it like that.

DR. SYMONS: Well, I think the key is occupational exposure to DMF regardless of the occupation. And if we look at the aircraft repairmen, it is very compelling to say that they used a solution that contained 80 percent DMF, that it was dripped onto exposed wiring in the aircraft and collected in vats just below the aircraft.

But as I noted, there are a lot of other exposures used in that occupation that weren't even addressed or discussed. And so it's kind of a coincidental thing to focus on one to the exclusion of the others.

With the leather workers, it's the same phenomenon. For those three index cases who worked as swabbers and had direct application of this DMF-based solvent to the leather tannery hides, it does seem, at surface, to be very compelling. But I think the NIOSH investigators do a very good report -- or a very good job reporting the industrial hygiene of the plant on basis of reconstructing that industrial hygiene.

As an epidemiologist working in occupational epidemiology, I'm very reliant on industrial hygienists and exposure assessors to provide me with those kind of

detailed information as to how processes are done and what are the potential for exposures. And I would say that, you know, the NIOSH report provides a lot of explicit detail, not only about the potential DMF exposure for those workers in the leather tanneries, but also many of the other chemicals that those workers may have come into contact with.

And I think the key piece of evidence here is the NIOSH conclusion that there was no report of acute symptoms that we traditionally associate with excessive DMF exposure. And those are documented in a study that we provided by Redlich, et al., investigators from Yale University.

So the lack of compelling evidence that showed that any of these abdominal pain, alcohol intolerance, or flush symptoms occurred in these workers gives us some circumstantial evidence that they were not overexposed.

CHAIRPERSON MACK: No, I understand that, yes.

But when they address the tannery exposures and their diversity, they were talking about all the tannery workers, not about these three guys that popped up in the first place, right?

Okay. Anyway, could you describe again the exposure that happens in the DuPont situation. Is there, in fact, open contact between the air and the liquid, or

is it all in a confined system?

DR. SYMONS: Well, in kind of a basic way, I can speak to that. But, you know, the details were -- obviously, the study was conducted many years ago, plants that are no longer producing Orlon fiber. So it's impossible for me to know the full extent. But DMF was used as a solvent in preparing the acrylonitrile. There were process changes over time. I don't immediately have those details accessible to me. But I believe that the industrial hygiene effort and the exposure assessment effort that was conducted to support the Chen studies was a very well validated documentation of potential exposures to DMF.

CHAIRPERSON MACK: Okay. Thank you.

I don't have any other questions.

Anybody else?

Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, thank you for your extensive presentation and for answering all the questions.

On your next to the last slide, that nice table of data you have of selected statistical tests for DuPont incidence study for cohort exposed only to DMF.

DR. SYMONS: Yes.

COMMITTEE MEMBER LANDOLPH: So is that a true

statement, exposed only to DMF, or are there other confounding exposures? Or is that just DMF?

DR. SYMONS: This table was prepared in response to what we received from OEHHA in the draft hazard review. Their appendix lists four tables, tables A-1 through A-4. And they use those tables to mirror the report in the Chen study where they break the cohort into subgroups. The first subgroup is those workers who are exposed only to DMF, 2,530 workers. There was another subgroup that had no DMF exposure, 1,130 workers. There was a subgroup that had DMF and acrylonitrile exposure. And then finally a combined DMF-only and DMF/acrylonitrile group, 3,859.

You know, again, because of many numbers of analyses, I wanted to focus really on the key ones that were at discussion here. And this slide was prepared off of OEHHA's Table A-1 to show the distinction between the chi-square P-values and the Poisson-based P-values as well as the 95 percent confidence intervals that come with the Standardized Incidence Ratios for those cancer diagnoses that had some circumstantial evidence of increased significance. And that's why we focus only on buccal/pharynx, melanoma, prostate, and stomach, because the remainder of the results, frankly, are not compelling.

COMMITTEE MEMBER LANDOLPH: Okay. And I looked at this table and I see four SIRs, all of which are

elevated above 1.

DR. SYMONS: Yes.

COMMITTEE MEMBER LANDOLPH: Three have not reached statistical significance, but the first one has and is at 5.6. So that data seems fairly positive to me.

And what is it that you don't like about that data?

DR. SYMONS: It's not a matter of liking or not liking. I think to put the inferences that we derive from these results into perspective, the buccal/pharynx cancer was definitely an elevated finding. It was much higher than observed. And that's why the researchers took the next step to document alcohol and specifically smoking of tobacco product usage in these 9 cases in this part of the cohort, but the 11 total that they found at the plant.

Again, the SIR in this study is based on a reference population of, what we call, the DuPont employee reference population. And this is a specific technique that we apply to our occupational epidemiology studies to remove the effects of what is known as the healthy worker effect bias. By focusing on a comparison between DuPont workers at the Camden, South Carolina, plant versus expected cancers based on the rest of the DuPont employee population, we're able to remove any kind of confounding effects due to external population comparisons due to

healthy workers.

So what this result for buccal/pharynx tells us is that, at this plant, we had a greater than expected occurrence of buccal/pharynx. Now, the next question is why. And I think, you know, that is a legitimate topic for further investigation, which is why it was pursued in the Walrath case control study. And, again, you know, the inference that we derived is whether or not buccal/pharynx would be related to DMF exposure. And that's again enhanced by understanding that all of these workers had significant tobacco usage for greater than 20 years.

For the melanomas, prostates and stomachs, though the SIRs are increased, again, we're talking about rarely occurring cancers. So three observed cancers for prostate, but you only had an expectation of 0.9, does lead to an excessive SIR. But because of the small numbers, the variability in that estimate, the confidence interval tells us that it's not a significant finding. And therefore, three prostate cancer diagnoses in a cohort of over 5,000 workers, though relatively increased, it's very difficult to draw any inference about the exposure relationship with that.

COMMITTEE MEMBER LANDOLPH: Thank you.

CHAIRPERSON MACK: Thank you very much. I think DuPont has done a really terrific job of providing the

information we needed. And it's a pleasure to have an epidemiologist come and address us, because usually that doesn't happen.

DR. SYMONS: Well, we're still few. But we're --

CHAIRPERSON MACK: That doesn't mean we're all on your side though.

(Laughter.)

DR. SYMONS: Well, I did want to note earlier, and interestingly enough, my former dissertation advisor I believe is joining you and your faculty at the University of Southern California. I studied under Dr. Jonathan Salmon.

CHAIRPERSON MACK: Okay. Now, let's go to the Committee's judgments. And let's hear from Sol.

CHIEF COUNSEL MONAHAN-CUMMINGS: Dr. Mack, just a --

CHAIRPERSON MACK: Oh, I'm sorry.

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm sorry. Just very quickly I just wanted to clarify something from the earlier slides that DuPont put up when Mr. Landfair was speaking. He was talking about the standard for listing under Prop 65 for this Committee. And he's absolutely accurate in terms of slides 3 and 4, where he's talking about what the statute and the regulations say about listing. And that is basically the same script that Dr.

Mack will use when you get to that point.

What I wanted to point out to you though is that Slide No. 5 is talking about the guidance criteria for the Committee. You have a copy of the guidance in your binder; and the second tab, I think it is, that says "Guidance Criteria." And I would just suggest to you that you might want to look at that in context. The quote there says chemicals should -- well, it's not a quote. There's a statement there, "Chemicals should be listed only..." -- and then there's a quote. And so I just wanted to be clear that if you look under D in the -- if you look under your tab for guidance and 1.D on the first page, the last sentence, you might want to read that actually in context, because I think it's stated in more mandatory terms here than it's actually intended in your guidance.

The other thing I wanted to mention to you is this is guidance. It was adopted by you, or at least predecessors of you, as Committee members. And so it isn't mandatory in the same sense as the statute and the regulations. So I just wanted to clarify that. I'm not saying there's anything wrong with it. I just want you to see it in context.

MR. LANDFAIR: If I could address that point briefly. First, I hope you don't find that misleading in

any way. "Only" is certainly my inserted word. It's not a part of the quote. So I didn't intend it as a misquote.

But, moreover, I think in context it is a perfectly accurate interpretation of the statute and the guidance, that if the criteria are to list a chemical if the weight of the evidence clearly shows that it causes cancer, then, conversely, we don't list a chemical unless it clearly shows; so therefore we list it only if the evidence clearly shows. And I hope that's understood and not perceived as any attempt to mislead.

I almost would like to -- I also would like to stick in one sentence of closing argument here that's pertinent to this.

You know, if the only data we had before us were the Senoh data, then notwithstanding the --

DIRECTOR DENTON: Stan, we're having a little problem hearing you. So maybe you could...

MR. LANDFAIR: If the only data we had before us were the Senoh data, then one might be tempted to conclude that it met the standing for listing. But under the circumstances, we think the question is, should the Senoh data be used as the basis for completely reversing all of the previous regulatory determinations on this chemical and the data that underlie them? Is the Senoh study so convincing, are we so sure that it's scientifically valid?

Are we not concerned about these identified flaws in the studies that we would disregard the previous findings of the IARC and the WHO indicating that the other data tend to show that it does not cause cancer? We've clearly got to do some balancing here.

And it's our view that the Senoh data, which are the only data to show carcinogenicity, just cannot support that type of conclusion.

CHAIRPERSON MACK: I'm sure you know that the deliberations at IARC/WHO are committee deliberations also, but in different -- there's one big difference; and, that is, there's a very big diversity of disciplines that are involved, and each has an equal vote. And, consequently, there may or may not be appreciation for the weight of the certain study. You emphasize weight. But weight is, of course, a matter of personal opinion and it's a matter of personal experience and discipline. So while we'd have greatest respect for IARC, we don't necessarily agree with everything they decide. So we will look at these issues very carefully and thoughtfully discuss them.

MR. LANDFAIR: I'm confident you will, and I want to thank you for the time and consideration you've given us. Thanks.

CHAIRPERSON MACK: Okay. Sol, I think we should

go ahead and discuss the animal data.

COMMITTEE MEMBER HAMBURG: I have to tell you, I've been very impressed with DuPont's analysis of the Senoh data. I think that -- I do see significant toxicity at the higher levels, 800 parts per million as well as 400 parts per million. I think the data is suspicious for having excess absorption of the DMF. I'm suspicious of the significant amount of hepatotoxicity that was noted; particularly at the lower levels of 200 parts per million, they saw significant amount of hepatotoxicity.

And I'm not convinced that the Senoh data is enough to undermine the other animal data. And I would agree with DuPont, that at this particular setting, I don't see that there's enough information to list DMF as a potential carcinogen.

The epidemiological data is weak as well, I believe. I think this is cluster data. Cluster data is very good for beginning to think about hypothetical causes of testicular cancer. I don't think the data's supportive or strong enough to suggest a conclusive carcinogenic potential of DMF. And I, for one, don't think that we should list this.

CHAIRPERSON MACK: Okay. Anna, what do you think about the epidemiologic data?

COMMITTEE MEMBER WU: Without rehashing, I think

the epidemiology data is limited. But I think it's certainly suggestive that there may be something. But I guess that the part that really was troubling to me was that, in fact, this was not followed up in any other way since the initial reports. And if this is still being in use, I think there is -- I think it's important that I should understand is the different routes of how this is being used. And I think some additional information from that angle would be helpful. But I think the -- I mean, I think that what is missing is really some additional insights as to, you know, occupational groups that are still exposed to this and what type of health outcomes, including cancer outcomes. So I think the Epi data is still limited.

CHAIRPERSON MACK: Is what?

COMMITTEE MEMBER WU: Still limited.

CHAIRPERSON MACK: Okay. Well, let's start over here on the end and hear from David.

COMMITTEE MEMBER EASTMOND: Sure. I mean, I think there's some certainly questions about the epidemiological data and how reliable that is. I see that as suggestive, as is common, written up in the document.

As far as the animal data, I think it's -- I mean, it clearly causes both benign and malignant tumors in the liver in both male and female mice and male and

female rats. So it's really pretty clear evidence in the Senoh study.

Now, the difference between these, in the mice certainly you've got a 24-month study, the Senoh study, versus the Malley study, which was an 18-month. And it appears that the early -- the tumors, and that's not uncommon to have increase of tumors at the very end kick in.

So the real question comes down to, has the maximum tolerated dose been exceeded? And that's a difficult one, because if you start saying, okay, well, if we eliminate the high dose in the rats -- the female rats, which we have mortality, and then start looking, you still have evidence of carcinogenic effects. And you even go to the lowest dose tested in this, for 200 ppm, you have an increase in cancer. So for me that indicates that, you know -- I don't see -- I can't really discount this. I don't see -- I see there could be potential problems with it because of the toxicity, but those aren't convincing to me. I don't think the species sensitivity issue is convincing. And, in essence, the high dose element where the question was brought up about the dosage, for me that's really kind of a dose response question rather than a hazard identification question.

So, for me, I think that the evidence is there

that it causes cancer in rodents.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: My views are similar to Dave's. I liked the -- I was intrigued by the data for liver tumor incidence in the male mice. It's dose dependent. It's statistically significant in the trend test for combined tumors, for hepatocellular carcinomas and hepatocellular adenomas. All follows a trend test and they're statistically significant.

In the females, the tumor data for hepatocellular adenomas and for hepatocellular carcinomas are dose dependent and statistically significant and the trend test is statistically significant. And for the combineds you get a dose-dependent statistically significant effect. So that's in male and female mice.

And a similar thing is true in rats in the Senoh study, where you get dose dependence for hepatocellular adenoma statistically significant; trend test is statistically significant; for hepatocellular carcinoma and for the combined the same thing is true. And the same thing is true in the female mice. So it's pretty clear to me that from the Senoh study, that data is pretty solid in terms of dose dependence, statistical significance, and trend test being statistically significant. So it's very difficult for me to argue that away or to ignore it, and I

really don't like to do that kind of thing.

And it looks like there is a -- certainly higher doses and longer exposure times. More experiments should be done. We never have enough data when we make these decisions because the research is not targeted toward answering these questions. But you've got to go with what you've got, and I think that data is good enough for me.

The epidemiology data, I think, is suggestive. The two of them together seem to suggest that DMF can be carcinogenic. So, I think, I know enough -- I never have enough data, but I know enough to make the decision I'm forced to make today.

CHAIRPERSON MACK: Thank you, Joe.

Marty.

COMMITTEE MEMBER HOPP: I think the epidemiologic data here in these clusters are very scary. But as Sol says, cluster data is always scary, and doesn't necessarily mean anything.

When I look at the epidemiology data of the other cohorts, I think the controls are weak. But it does seem to suggest to me, when I analyze this, that this is a -- DMF is an additive, a solvent that enhances carcinogenicity. I don't see any direct carcinogenicity in these epidemiology studies. It appears to me to be more of an enhancer than causing cancer in humans.

The Senoh study at 200 milligrams really bothers me a lot. The increased tumors in mice at that level is hard to discount, because at a lower level, even with all the testing data and the booth -- if you assume that the concentration that they claim they get is wrong as produced by DuPont and that, in fact, aerosolization and other means has a higher concentration in the animals, still at 200 you would expect to have a lower incidence of those tumors. And it's very bothersome to me, at that lower incidence, to have such a high incidence of tumors in those mice. It's hard to discount that data to me.

So, I think, to the humans, it's not very clear. If anything, it seems to be about a co-carcinogen or a promoter in the animal data. You know, often promoters can be carcinogenic or at least be so toxic they become carcinogenic. But that 200 milligram level is very bothersome to me.

CHAIRPERSON MACK: Darryl.

COMMITTEE MEMBER HUNTER: I'm unconvinced that the data that's presented today warrants listing this as a carcinogenic agent. And, hopefully, I haven't put you to sleep with my long opinion.

(Laughter.)

CHAIRPERSON MACK: Well, I found this actually pretty tough, because I think there's lots of little

evidences on both sides.

With respect to the epidemiology, I think that the -- I can't get excited about the results of the DuPont studies, although it does -- the throat issue does bother me a bit. But the general probable relatively low level of exposure and the relatively limited follow-up tell me that maybe there is something there, but we don't have enough data to be sure.

The controls for the tannery analytic studies I think are, as you have pointed out quite well, are pretty bad. The age difference, the difference in the way the questions were asked, I'm not convinced by that.

So what sticks in my craw from the epidemiology is, I hate to say it, but it is the clusters. It's not the presence of a single cluster of three testis cancers in a Naval unit. And it's not the presence of three in a tannery unit. Although the two together add up.

But the fact is that the guy who looked at the other Naval station where they were looking at the same exposures found another set of four testis cancers. That to me is the most difficult to completely wash away.

So I think there is something in the epidemiology. I grant you that it isn't anything that's going to win a Nobel prize, but it's hard for me to avoid it.

When I look at the animal data, I don't see the letters MTD anywhere in the Prop 65 language. So, there are lots of ways to discuss whether or not the mechanism is this or that. And my attitude toward causation is that -- the one definition of cause is if the outcome doesn't occur when the exposure isn't there, that's the cause. And that's the only criteria. Whether it's acting by virtue of genotoxicity or promoting transmission through a membrane or whatever, it doesn't make much difference.

And so I can't get excited about washing away the animal studies by virtue of the excessive dose and the presumption that these studies are not reflective of what would happen with mice, if they were given the drug under other circumstances. Because the fact is that the only reason we use animal studies is because they are -- the only reason we use them is because we have to. And we know full well in using them that they are not representative of what's going to happen in people. They're only a suggestion. But the suggestion is imprinted in the Prop 65 language and so I think we have to follow it.

So I'm afraid I think that this chemical did cause liver tumors in rats and mice. And by virtue of the fact that it did so, I think we don't have any choice but

to list it, even though it may have caused them under unusual circumstances.

So that's my bottom line, I guess.

So does anybody want to discuss things further?

COMMITTEE MEMBER HOPP: No.

CHAIRPERSON MACK: Did I hear a no?

COMMITTEE MEMBER HOPP: No, you heard a -- you know, I think this -- whoever put together the guidance criteria in this booklet, I'll have to thank, because it's very, very helpful when I looked at it before. It kind of condensed all of our discussions that we've had in the past and had to bring out old -- our records, and now we have a very good guideline as to the conclusions we came to with these questions that, you know, we really do face repeatedly.

CHAIRPERSON MACK: We do try to use the weight of evidence and we do try to use clearly shown and we do try to use standardly accepted procedures. If I've misused the words a little bit, you know what I mean.

But the fact is that these are all personal judgments. And the only reason there's a committee is because it comes down to a judgment from a group of individuals who are trying to do their best to interpret the evidence. And so now we're going to find out what the actual result is.

So the way I have to word that is, Has N,N-Dimethylformamide been clearly shown through scientifically valid testing, according to generally accepted principles to cause cancer?

So all those voting yes to that statement, please raise your hand.

(Hands raised.)

CHAIRPERSON MACK: 1, 2, 3.

All those voting no, please raise your hand.

(Hands raised.)

CHAIRPERSON MACK: 1, 2, 3, 4.

The "noes" have it.

Are there any abstentions?

No abstentions.

We have decided not to list N,N-Dimethylformamide on the Prop 65 list.

Shall we go onto the next one?

Well, that was easy.

(Laughter.)

CHAIRPERSON MACK: Okay. That's a good question.

Do we want to take a break for lunch or do we want to charge through the agenda?

We think that TNT probably will not take as much time as this did. And we anticipate that the next question won't either. So should we go ahead and proceed?

COMMITTEE MEMBER EASTMOND: I'd just like to slip out for just a second and make a phone call.

CHAIRPERSON MACK: Another bathroom visit?

COMMITTEE MEMBER EASTMOND: No, it's a phone call this time.

CHAIRPERSON MACK: Okay. Ten minute --

COMMITTEE MEMBER EASTMOND: No, we don't have to -- I'll just go out of the room for two minutes.

CHAIRPERSON MACK: Let's take a ten-minute

(Thereupon a recess was taken.)

CHAIRPERSON MACK: Okay. Martha, you want to introduce Dr. Li?

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Yes. I'd like to introduce the presenters today for the TNT document. And the main presenter will be Dr. Kate Li. And talking about the epidemiology, the author of that portion of the document is Dr. Jay Beaumont.

(Thereupon an overhead presentation was

Presented as follows.)

DR. LI: Okay. I'm going to start a carcinogenicity review of 2,4,6-Trinitrotoluene, or TNT, which belongs to the chemical class of polynitroaromatic hydrocarbon.

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DR. LI: So, TNT is used as explosives in

military and industrial applications, including munitions, coal/mineral mining, deep well and underwater blasting, building demolitions. It's also used as a chemical intermediate in the manufacturing of dyes and photographic chemicals. It might occur in soil and surface and groundwater near munition facilities and sites of waste disposal.

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DR. LI: So here is the overall available carcinogenicity studies of TNT. In humans, there is one ecological study one case-control study, one cohort study, and several case reports available.

In animals, there are two studies in rats and two studies in mice, which are detailed here. Two-year dietary studies in male and female rats and two-year dietary studies in male and female mice.

Here I will pass to Dr. Jay Beaumont for the Epi review.

(Thereupon an overhead presentation was Presented as follows.)

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DR. BEAUMONT: There have been three epidemiologic publications regarding TNT-exposed workers. And the first by Kolb, et al., started as an apparent cluster. And we talked about the merits of clusters a

little bit this morning. But that's how this story started. In Germany, at the University of Marburg at a hematological clinic the medical people there noticed what seemed like a large number of leukemias, especially from the nearby town of Stadtallendorf. And they conducted an ecological study in which they compared their rates of AML and CML. It was myelogenous leukemia that seemed to be elevated. And they compared the rates in the City of Stadtallendorf with a nearby county called Giessen County, that did not have any TNT exposure.

I forgot to mention that in this town of Stadtallendorf there were two major munitions factories operated by the Germans in the period 1937 to 1945, with the highest production in the 1941-45 period. And they were said to have released a great amount of wastewater containing TNT that percolated into the soil locally, but also was sent out through a channel that went through another town that will come up in a little bit later.

And you'll see in this slide the results of their ecological study. They presented the results separately from men and women for acute myelogenous leukemia. They found an elevated risk in both men and women in the range of -- or ratio of 3.2 to 3.5, and both statistically significant judging from the confidence interval.

For CML, they found an elevated risk --

significant elevated risk in men but not women. And there was some problem with small numbers, that the CML ratio for women was based upon just one case in the exposed city.

Then about eight years later a group of investigators headed by Kilian, et al., did a study in the same area of Germany. And based upon the hypothesis that they said it was generated by Kolb, et al., they did a case-control study of 18 communities in that general area that included Stadtallendorf, but also another community called Kirchhain through which this TNT wastewater flowed in the channel that they called the long channel. So 2 of the communities had TNT exposure and the 16 others did not. And that was the basis of their exposure/nonexposure classification in their case-control study.

And they reported just two categories of cancer: All leukemia combined and then chronic myelogenous leukemia only, which also included MDS, myelodysplastic syndrome.

And not on the slide is the fact that the town of Stadtallendorf, that generated the hypothesis, they found no excess risk. And the only excess risk that they did find was in one neighborhood of the town of Kirchhain, where the neighborhood was located right next to that canal that conducted the wastewater with TNT in it. And

those are the relative -- or odds ratios that you see on the slide. And they're significant for both all leukemia and CML only.

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DR. BEAUMONT: Then the first data is out of China, a historical cohort study based upon workers at eight munitions plants, two of which manufactured TNT and six of which used TNT. And they looked at both incidence rates and mortality rates. For incidence rates, they compared to other workers at the same eight factories who were not exposed to TNT. For the mortality analysis, they compared the TNT worker rates to Chinese national rates for medium- to large-sized cities.

They reported results only for liver cancer despite -- they reported rate ratio estimates only for liver cancer, despite the fact that they reported the numbers of cancers for, I think, 16 different specific cancer categories. And they didn't say why they only reported rate ratios for liver cancer. Maybe because it was the most common cancer. And liver cancer is a very common cancer in China. There's a high background rate.

Anyway, so for liver cancer, in the incidence part of the study, overall they found a rate ratio of 3.46, which was significant at the .01 level. They did not report confidence intervals. And for the mortality

analysis, it was also about a threefold risk and equally significant.

I mentioned that there is a high background rate of liver cancer. We don't know if that enters into this. And we know that there are risk factors for liver cancer that they could not take into account, such as Hepatitis B infection, a virus infection in aflatoxin exposure.

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DR. BEAUMONT: And then last, and maybe least, are the case reports, of which there have been quite a few. And they've all been about either liver cancer or leukemia. And so one case of liver cancer was reported by Garfinkel. And then nine cases were reported by investigators in China. And you can see those reports listed.

And then, finally, there have been two articles reporting cases of leukemia, one case each.

And that's it for the epidemiologic evidence.

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DR. LI: So now I'll review the animal carcinogenicity evidence.

So in the study conducted by Furedi of U.S. Army lab, et al, and in a two-year dietary exposure of TNT study in female Fisher 344 rats, there's a significant increase in urinary bladder tumors. And one note here is

urinary bladder tumor, it's a rare tumor in rats -- in female rats. Referring to the NTP historical controls, the incidence rates is 2 out of probably 900 control animals.

So here we look at the data. Urinary bladder carcinoma in a control is 0 out of 54. Plus, in the highest dose group, it's 12 out of 55, which is statistically significant. In a combination of papilloma and carcinoma, the incidence is 0 out of 54 in controls and 17 out of 55 in the highest dose group.

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DR. LI: And there's no treatment-related tumor in the male rats in the two-years dietary study of male rats.

So the study carried also by Furedi, et al., of U.S. Army lab, and in mice, B6C3F1 mice strains, there's a significant dose-dependent increase in leukemia and malignant lymphoma of the spleen in female mice. And the trend is statistically significant.

And as we see here, there's 9 out of 54 in the controls. And in the highest dose group, the incidence is 21 out of 54, which is statistically significant. Again, there's no tumors induced in the male mice two-year study.

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DR. LI: So in summary, in animals, rare urinary

bladder carcinomas and papillomas were induced in female Fisher rats upon TNT exposure. And leukemia and malignant lymphomas of the spleen were induced in female mice.

There is no treatment-related tumors observed in male rats or male mice.

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DR. LI: Now I'll move onto the other relevant data. I'll summarize results from pharmacokinetics and metabolism study and genotoxicity study and structure activity comparisons with Prop 65 carcinogens, which I'll show you here.

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DR. LI: So PK and metabolism. TNT might be absorbed in gastrointestinal tract, skin and lungs, through oral and water intake, skin dermal contacts, or respiration.

TNT might be distributed primarily through the liver, kidneys, lungs, and fat tissues.

It might be eliminated primarily via urinary excretion. Or the biliary excretion, it's another route being reported.

Metabolism of TNT. Two major pathways have been reported. Nitroreduction of the aromatic nitro groups of TNT to form hydroxylamino derivatives. That's one of the pathways. The other pathway is through the oxidation of

methyl group to form benzyl alcohol and benzoic acid derivatives.

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DR. LI: This is a diagram that described the nitroreduction metabolism pathway. As we can see here, the top is the TNT may be metabolized to hydroxyl aminodinitrotoluene, the two derivatives. And then it may further reduce to aminodinitrotoluene here and here. And then to form the diaminonitrotoluene. That's what we have here. And also I want to indicate here hydroxyl aminodinitrotoluene might form reactive metabolites which have protein binding activity.

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DR. LI: So genotoxicity of TNT. As we see in this slide, in bacterial systems TNT showed positive responses in multiple strains of salmonellas and in the AMES Reversed Mutation Assays. And this indicates either -- frameshift mutation or basepair substitution. And these activities might occur in the presence or absence of metabolic activation. And an additional study also reported that these activities might require nitroreductase and o-acetyltransferase activity.

In E. coli SOS chromotest assay, TNT shows positive response in the presence of human placenta microsomal system. But negative results were found in the

presence of rat liver S9 system.

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DR. LI: In mammalian system in vitro, here we see TNT actually shows negative response in the rat liver in vitro UDS Unscheduled DNA Synthesis assay.

TNT is positive in the mouse P388 lymphoma TK locus mutation assay in the absence of S9. I want to indicate here this TK locus mutation assay, they test both mutation and also clastogenicity.

In hamster cells TNT show positive results in the Chinese hamster ovary HPRT mutation assay, either in the presence or absence of metabolic activation. But it's negative in a V79 cell HGPRT mutation assay.

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DR. LI: In mammalian system in vivo, this study we summarize here. In the rats, TNT is negative in the rat liver UDS assay and the bone marrow cytogenetic damage assay. And positive response, as we have here, is TNT induced oxidative DNA damage through formation of oxo -- deoxyguanosine in the rat sperm cells.

In mouse, a negative result was found in a bone marrow micronucleus assay.

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DR. LI: And one study in workers through occupational exposure to TNT has reported TNT genotoxicity

in humans. What they found is there's no difference between exposed and control workers in the level of chromosomal aberrations in peripheral blood lymphocytes. However, among the exposed workers, there was increased chromosomal aberration in the n-acetyltransferase 1 rapid genotype versus the slow acetylator genotype.

Among the NAT1 rapid acetylator genotypes, increase in the level of chromosomal aberration is found to be associated with glutathione S transferase M1 null or T1 null genotypes.

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DR. LI: So I describe to you a nitroreduction pathway of TNT metabolism. Here is a summary of genotoxicity of TNT metabolites. This would list here these four metabolites -- aminodinitrotoluene and also diaminonitrotoluene. They are all positive in the AMES salmonella reverse mutation assay. And the 4-aminodinitrotoluene also show positive response in the Chinese hamster ovary HPRT mutation in the presence of metabolic activation of rat S9 system. And it show a weak response in the hamster V79-HGPRT mutation assay. And the 2,6-diaminonitrotoluene also show a weak positive response in the Chinese hamster ovary HPRT assay.

So going down, also look at the hydroxyl aminodinitrotoluene, the first level of nitroreduction

metabolite and it can actually induce in vitro oxidative DNA damage through cleavage of DNA at the sites with consecutive guanines and form 8-oxo deoxyguanosine.

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DR. LI: Urine mutagenicity has been reported in rats treated with TNT. And urine is positive in the salmonella mutation assay.

In workers exposed to TNT, increased mutagenicity in AMES test -- or salmonella test of the urine has been found. And also there's a higher mutagenicity activity in the NAT1 rapid genotype versus the slow acetylator genotype.

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DR. LI: Structure activity comparisons. TNT, it's compared to a number of structurally similar Prop 65 listed carcinogens. The 2,6-dinitrotoluene, 2,4-dinitrotoluene, and 2-nitrotoluene, as we see here, these three chemicals induce tumors -- a variety of tumors in rats and/or mice. And they all have the DNA and protein bonding activity. TNT apparently does not share the tumor sites with these chemicals.

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DR. LI: Potential mechanisms of TNT carcinogenicity may act through a genotoxicity mechanism either by mutation or induction of oxidative DNA damage.

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DR. LI: Here are authoritative body reviews. In 1993 U.S. EPA has defined TNT as a Group C chemical, which notice possible human carcinogen. U.S. EPA reviewed animal studies by Furedi, which is the U.S. Army lab. And, however, they did not include any human studies. And also several studies on metabolism, genotoxicity and biomarkers of exposure were not included.

In 1996, IARC classified TNT as a Group 3 chemical, which is not classifiable as to carcinogenicity in humans. IARC did not include Epi studies of Kilian, et al., and Yan, et al., which is published after 2001.

And IARC also did not include animal cancer studies, because that's by the U.S. Army lab. It's not in a peer review -- it's not published in a peer review journal. And they did not include several recent studies on metabolism, genotoxicity, and biomarkers of exposure.

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DR. LI: So, in summary, the evidence of TNT carcinogenicity in humans is not adequately studied. However, it is suggested that TNT might induce liver cancer and leukemia based on the case reports and control studies.

In animals, rare urinary bladder tumors in female rats. And leukemia and malignant lymphomas of the spleen

in female mice were reported.

Other relevant evidence include genotoxicity of TNT and its metabolites. And also I show you the structure similarity of TNT to the carcinogens 2-nitrotoluene, 2,4- and 2,6-dinitrotoluene.

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DR. LI: So thank you for your attention.

CHAIRPERSON MACK: Thank you, Dr. Li.

Does anybody on the panel have any questions for either of the presenters?

I guess you did a really good job.

COMMITTEE MEMBER HOPP: I have a question.

CHAIRPERSON MACK: Oh, Marty.

COMMITTEE MEMBER HOPP: In this study on the female rats for leukemia and malignant lymphoma, do you have any comment about the high incidence of tumors in the no dose of -- when TNT was zero?

DR. LI: Tumors of -- you're talking about control studies.

COMMITTEE MEMBER HOPP: Furedi's study of TNT dosage to regions in the female mice.

DR. LI: Yes. Yeah, the controls -- yeah, they have -- what we have is a summary of their report, and they report those numbers there in the summary. They didn't mention the historical controls.

COMMITTEE MEMBER HOPP: Well, in the ones that received zero dosage, one-sixth of them got tumors.

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: That's correct. There's a spontaneous background rate of leukemias and lymphomas in mice as they age. But what is being seen is a treatment-related effect increasing with dose. But you're correct, that there is a background rate, much like we've seen with other studies with liver tumors.

CHAIRPERSON MACK: Any other questions?

COMMITTEE MEMBER WU: I just have a question about the liver cancer study in China. Where was -- where was the cohort -- how was the cohort put together and where was that cohort? You may have mentioned it. I just missed it.

DR. BEAUMONT: Actually, the investigators did not say where geographically in China these eight munitions factories were. They just said that there were eight factories. Was that all of your question? I can't remember.

DR. LI: I remember, yes, there are seven or eight factories. They locate in the northern part. But they are very sparsely distributed.

CHAIRPERSON MACK: The difficulty is that liver cancer is --

DR. LI: Not in the past operations --

CHAIRPERSON MACK: -- very non-randomly distributed. In the south coast of China there's huge incidence rates. And so it would be very interesting to know where it was.

DR. LI: Yeah.

CHAIRPERSON MACK: Presumably because of Hepatitis B.

DR. LI: These are in the northern part. And they are sparse to northern east to kind of west of the country, if I remember the location they mentioned.

CHAIRPERSON MACK: Any other questions?

COMMITTEE MEMBER HUNTER: Aging male rats and mice don't get malignant lymphomas and leukemias?

DR. LI: Aging rats or aging mice?

COMMITTEE MEMBER HUNTER: Well, the mice and rats, they were all females that were studied. An earlier question referred to, as they aged there's a certain background the amount that are going to develop these malignancies. Are they not known to be in male rats and mice? Why is this phenomenon being seen in females?

DR. LI: Yeah, that's actually a good question. The male rats, they do observe liver hyperplasia and also, if I remember, adenomas, but they're not significant. And you'd talk about a -- leukemia and lymphoma in rats,

apparently there's no like incidence of that. They did inspect a number of tissues for both rats and mice, but that's not the situation -- not the case in rats for leukemia and lymphomas.

In mice, the background has already been mentioned. Spontaneous when they age. There are instances of leukemia and lymphoma in the controls.

COMMITTEE MEMBER HUNTER: So, I mean, is there -- there are no studies that looked at this in the male gender at all? It would seem like zero would be an excellent control rate, if --

DR. LI: The studies cover -- actually, I mentioned in the previous slide, there are two studies in rats, one in male rats, another in female rats in parallel. Basically, the dosing conditions, everything were the same. But they did not observe this tumor. That's why it wasn't reported. I did not report it here.

And the same for the mice study. There are two studies. One in male mice, another in female mice. In male mice there's no significant increase of treatment-related tumors. That's what we summarize.

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: So maybe if I can clarify. It's most likely that indeed they saw some lymphomas and leukemias in male mice in the control and all the treated groups, but they didn't

see any difference in the incidence between the groups, so they did not report that data, because they saw it -- there's no difference between treatment and control groups. Therefore, there's no effect at that site of treatment. What the investigators were looking for were sites where there seemed to be a difference in tumor incidence between the treatment groups and the controls.

CHAIRPERSON MACK: Anybody else?

DR. BEAUMONT: Excuse me. I'd like to add just a little bit more to Dr. Wu's question. I remember she also asked how the cohort was put together. And the authors of the article did not give any detail, except to say that all the workers were employed for at least one year in the time period 1970 through 1995, and they were followed up for cancer through '95, so some had a very short observation period. They gave no details on the follow-up as to how they determined who had died or gotten cancer. And no statistics on what their success rate was on following up workers, which we normally see in a cohort study. So there weren't a lot of details.

And we did estimate, I should add, that even if we -- if the excess liver cancers were subtracted out, it would still appear to be an almost doubled rate of cancer overall in this group of workers that's not explained.

So there might be some methodological issues, but

I think that might have been the basis of your question.

COMMITTEE MEMBER WU: Thank you.

CHAIRPERSON MACK: Any more questions?

David.

COMMITTEE MEMBER EASTMOND: I have a general question that's actually not directly in your document. But in the original report there's lymphomas which -- leukemias and lymphomas which are found in the spleen. There's also some increase, almost -- a little bit -- about a doubling of leukemias and lymphomas, which was found in the kidney.

Just for clarification, is it common to split these out? I know sometimes they keep them separate by organ or to combining those. How does -- do you have any thoughts about that? It was not a statistically significant increase within the kidney, but it was slightly elevated.

DR. LI: I have a book chapter here that describes about a lympho-hematopoietic system tumors.

And what they define here, it's for, what they call, malignant leukemia origin from a certain organ. They do not combine them.

That's a simple way of explaining that.

And it might be origin from several major sites, for example, lymph nodes and thyroids and also the liver

and spleen and kidneys -- this one is not to described in the book chapter. However, this separately described by the investigator in the Furedi, et al., study, which is consistent with the classification system. Prior to '91, they have an old classification system. And also in '94 they redescribed the -- they're pretty consistent, in other words, how you classify leukemia and lymphoma and when they are the origin for an uncertain organ, they do not combine them naturally.

COMMITTEE MEMBER EASTMOND: Okay.

CHAIRPERSON MACK: Okay. Is there any more questions?

I gather there are no public comments available on this material?

I guess not.

Then it comes to the Committee to decide. And we, of course, are very concerned about this product, because we don't want little kids to be going around it if they can avoid it and get cancer from it.

So let's go ahead and begin with David. And give us your comments on the animal studies.

COMMITTEE MEMBER EASTMOND: Well, they're pretty much summarized in the document. The key point of this is -- again, there were two-year chronic studies, which were done by contract laboratories, but they were

sponsored by the Army. And in the summary reports that were provided, essentially they only provide -- present the data for where they think there may be an association with exposure. So you don't have a lot of the background incidence.

But there's a clear increase in papillomas and carcinomas of the urinary bladder seen in female Fisher 344 rats. And as indicated, it's a dose-related increase. The spontaneous incidence of these tumors is actually quite low, so it's a fairly rare tumor.

And I will say that it's actually occurring at relatively low doses. You know, the high dose is 50 milligrams per kilogram. When you're talking with rat bladder carcinogens, that's relatively low. Most rat bladder carcinogens kick in at much higher doses from my experience.

So it looks like we have a rare tumor and clear-cut increase in the female Fisher 344 rats.

As indicated in the female B6C3F1 mice, there was a dose-related increase, although it was not too impressive -- it was relatively weak -- but a little over a doubling the incidence of leukemias and lymphomas that was seen in the B6C3F1 mice, the females. So, again, there is -- this is a tumor site, which has somewhat elevated incidence in the controls. But it does appear

there is a dose-related increase seen with increase in doses of TNT.

So, in essence, we have clear increases of the cancer in the urinary bladder in the rats and we have apparent increase in the mice. And so it's in different species, both in females.

CHAIRPERSON MACK: Thank you, David.

I'm supposed to be the epidemiologic person on this, and that's a pretty easy job.

Going backwards, we certainly can't learn anything from the case-control studies. And I think that the Yan study is so confounded, especially by Hepatitis B, but also by aflatoxin, and God knows what else, that it's impossible to interpret it. So I don't think that provides any information.

And I think the same is true of the German studies, because there is the kind of cluster report. And a follow-up does exactly what we expect from cluster reports, namely, it's a matter of following your own nose. If you decide that it's A then in the first place, you're going to find A in the second place because that's the only thing you look for.

So, I think there is no epidemiologic data and the decision will rest solely on the animal data.

So now let's go to Joe.

COMMITTEE MEMBER LANDOLPH: Yeah, I agree with everything Dave said on the animal studies. The female Fisher 344 rats data was very clean, near zero tumors in the controls. And the data is very high at the high dose and it's statistically significant. The trend test is positive. And you get a statistical significance in the female mice for the leukemias and lymphomas. It's dose dependent, statistically significant, and the trend test works.

And then the other thing that's interesting about this, you got lots of genotoxicity data. So this is more comfortable to deal with than the other one we dealt with. Lots of AMES positive data, as was already pointed out. You've got positive E. coli data. You've got positive oxidative damage data, hydroxydeoxyguanosine. You've got positive P388 lymphoma, TK locus mutation data. You've got CHO-HGPRT mutation data. So it's very good mammalian data.

And then, in addition, they've got some genotoxicity in humans, where you've got increased chromosomal aberrations in rapid versus slow acetylators and increased chromosomal aberrations with the GSTM null or GSTT1 null phenotypes. And the metabolites are positive. You know, the metabolic scheme, you've got reduction of the nitro groups to amino groups and then

P450 activation of those.

There's even data that this compound or its metabolites bind to hemoglobin in humans, which indicates it's very likely to bind to the DNA in humans.

So this all fits together pretty well for me from the animal carcinogenesis study and then the genotoxicity study and the binding to hemoglobin in the humans. So it's clearly a genotoxic carcinogen metabolized through nitroreductase and P450s and it's going to bind to DNA. And you've got animal tumor data in two different species, as Dave pointed out. So it's straightforward for me.

CHAIRPERSON MACK: Thank you, Joe.

Marty.

COMMITTEE MEMBER HOPP: There's a limited amount of things you can say about four studies. But I think the epidemiological studies are disappointing, because you'd think such a common material would have some more epidemiological studies, the workers and stuff. And so it's surprising there isn't more data regarding that.

The animal studies, you know, I'm concerned regarding the high incidence of leukemias and lymphomas in the zero dosage. But the trend is very clear. But starting out so high, it kind of bothers me a little bit. But bladder tumors, kind of a soft spot for that. And I think it's very clear relative to the bladder tumors.

Genotoxicity, it's fairly straightforward. But more impressive to me is the metabolites that come out of it that seem to be very toxic to me and carcinogenic to me.

CHAIRPERSON MACK: Anna.

COMMITTEE MEMBER WU: I don't really have anything else to add. You know, I think, I agree with what's been said about the Epi studies, and I'll defer to the --

CHAIRPERSON MACK: Sol.

COMMITTEE MEMBER HAMBURG: I would like to agree with Anna, that I don't have anything to really add. But I would say I'm not surprised that there's not more data about TNT, since there's a secondary motivation to keep TNT underground.

(Laughter.)

CHAIRPERSON MACK: Darryl.

COMMITTEE MEMBER HUNTER: I'd like to add that I also have nothing to add.

(Laughter.)

CHAIRPERSON MACK: Okay. Let me find my envelope here.

CHAIRPERSON MACK: Has 2,4,6-Trinitrotoluene been clearly shown, through scientifically valid testing according to generally accepted principles, to cause

cancer?

So now I'm calling for "yes" votes. Raise your hand for yes.

(Hands raised.)

CHAIRPERSON MACK: My God, we're unanimous.

No "no" votes and no abstinence.

So the answer is, yes, we are deciding that this compound should be listed.

Oh, that was easy.

(Laughter.)

CHAIRPERSON MACK: Now, we're going to have a preamble to the next section?

CHIEF COUNSEL MONAHAN-CUMMINGS: I'm just going to get the slides up. Just a second.

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: I think we're having technical difficulties. It's not responding.

There it is.

CHIEF COUNSEL MONAHAN-CUMMINGS: All right. This is Carol Monahan-Cummings, the Chief Counsel for OEHHA and counsel for the Committee. And I just wanted to explain to you what this particular item is about. It's one that you probably haven't seen before for this group of the Committee. This particular task has been done by OEHHA in the more recent past.

But originally the statute and the implementing regulations for Prop 65 actually say that the State's qualified experts have to do this task, and so that's why we've got it in front of you today.

The statute -- and a lot of people don't know this -- actually requires the Governor to publish two lists. Okay, the one that you were -- that has a lot more impact and you get a lot more input on is the list of chemicals known to cause cancer or reproductive effects. And that was what you were talking about the individual chemicals this morning and earlier this afternoon.

This list, the second list that's required under Prop 65, is a list of chemicals that are required by State or federal law to be tested for potential -- for their potential to cause cancer or reproductive toxicity, but which have not yet been adequately tested as required. So what this really means is that there are certain federal and State laws that require certain chemicals to be tested for their potential to cause cancer or reproductive effects. These are specifically State laws known as the Birth Defect Prevention Act; federal TSCA, which is the Toxic Substances Control Act; and the federal FIFRA, which is the Federal -- let's see if I can say it correctly -- Insecticide, Fungicide, and Rodenticide Act, which is -- it's a federal law, but it's also enforced in California

by the Department of Pesticide Regulation.

Okay. So, under the statute and our regulations, every year OEHHA contacts U.S. EPA and the California Department of Pesticide Regulation and asks them to look at the list that's already in the regulations, formerly Section 1400, now Section 2700 and -- or 27000, I'm sorry -- and we ask each of those agencies to tell us whether there are any chemicals that are currently on our list, that they now have all of the adequate testing, each of the studies that they need have been provided to them and are of adequate quality. And, if so, they tell us so that we can take those chemicals off the list or at least take off those requirements for certain kinds of testing to be done.

And we also ask them if there's any additional chemicals that should be added now to those lists, because they're required to be tested. Okay?

So each year we do that. We gave you a copy of the existing list. These materials should be in your materials that you got today. I apologize, they went out to you a little bit late, and so I sent them to you via Email and then snail mail, and we also gave you a copy today.

Is it in the blue binder, Cindy?

DIRECTOR DENTON: Yeah, they're there.

CHIEF COUNSEL MONAHAN-CUMMINGS: Okay. So what we gave you, there's a copy of the existing regulation, which hopefully looks like this. It says the Excerpt of Section 1400.

Can you see that there?

And then we also gave you copies of the letters that we had sent to U.S. EPA and to the California Department of Pesticide Regulation asking them for updates. And it included their responses. And then we gave you a draft of the changes we'd like to make in the regulation that is based on the information that they provided us.

If you'd go to the next slide.

(Thereupon an overhead presentation was Presented as follows.)

CHIEF COUNSEL MONAHAN-CUMMINGS: To make this a little bit easier, for you so you don't have to go through the list to figure out what is being struck out and what's being added, we've got a list here, which we'll provide to you. And I'll give it to the court reporter as well.

The first list being -- yes.

COMMITTEE MEMBER EASTMOND: Can I just clarify something?

CHIEF COUNSEL MONAHAN-CUMMINGS: Sure.

COMMITTEE MEMBER EASTMOND: In this case, you're

talking about the list of chemicals that need to be tested or additional information?

CHIEF COUNSEL MONAHAN-CUMMINGS: Right.

COMMITTEE MEMBER EASTMOND: So it's not the list that we talked about, the --

CHIEF COUNSEL MONAHAN-CUMMINGS: No.

COMMITTEE MEMBER EASTMOND: -- Proposition 65 list?

Okay. So it's just --

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, it is a Prop 65 --

COMMITTEE MEMBER EASTMOND: Yeah, but it's not usual --

CHIEF COUNSEL MONAHAN-CUMMINGS: Right, it's a much --

COMMITTEE MEMBER EASTMOND: So this is this compilation here. Okay.

CHIEF COUNSEL MONAHAN-CUMMINGS: Right, right.

And this list does not -- in this case, you're not determining that any of these chemicals cause cancer. What you're trying to do is determine whether the chemicals still need to be tested to find out if they cause cancer.

And there's only a certain number of chemicals that are actually required to be tested. And those are --

U.S. EPA and DPR keeps track of those.

Because the testing has to be done and provided to them for their decisions like on registration of a pesticide or re-registration of a pesticide or -- under TSCA.

So what we have for you is we basically have put together two lists. One, this list that's up on the screen now of five chemicals that U.S. EPA is asking for us to add to a list of chemicals that still need to be tested. And we'll -- Cindy, maybe if you wouldn't mind passing those out.

We're calling that Exhibit A for the record. And I'm going to provide a copy of that to the court reporter, because I don't want to try and pronounce these chemical names.

So we have Exhibit A, which is the list of chemicals that we're suggesting -- that U.S. EPA wants to add to the list.

And we have Exhibit B, which is 48 chemicals that primarily U.S. EPA, but also DPR, have determined they've received the testing for all of the cancer. And when that repro testing is complete, then they can be removed from this list. Now, that's not a finding that these chemicals once again either cause or don't cause harm. It's just a finding that now U.S. EPA and DPR have the test data that

they need for their program. Okay?

So what I'd like to do -- I certainly can answer your questions here. But this is basically a ministerial act on your part. We just want to be able to update the list that's in the regulation based on the information that's provided from the U.S. EPA. And you can rely on that because it's their program, so you don't have to make independent scientific finding in regard to these chemicals. We're just needing to update the list, and it's supposed to be done by a finding by this group.

So what I'd like to do is have Dr. Mack --

CHAIRPERSON MACK: Why don't I first ask if there are any questions.

CHIEF COUNSEL MONAHAN-CUMMINGS: Sure. Okay.

CHAIRPERSON MACK: How long is the list to which these five are to be added?

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, it's in the materials that you have there. Right now, there's --

CHAIRPERSON MACK: Well, I see the list of ones that have been adequately tested by EPA. So that's the next list. But is there a list --

CHIEF COUNSEL MONAHAN-CUMMINGS: Right. These two -- the Exhibit A and Exhibit B are the changes we want to make. But the existing list that's in the regulation is in the materials that you were provided. It's --

(Thereupon Exhibits A and B were marked.)

CHAIRPERSON MACK: So the one that has a lot of them crossed out, we assume that the ones that aren't crossed out are the ones that remain on the list, and these five will be added to that; is that correct?

CHIEF COUNSEL MONAHAN-CUMMINGS: Right, that's correct.

CHAIRPERSON MACK: And is it also correct that our expertise in this matter is of no use whatever?

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: Well, unfortunately I think that kind of sums it up.

(Laughter.)

CHIEF COUNSEL MONAHAN-CUMMINGS: I don't think that we're asking you to make a scientific determination. The statute isn't clear on what criteria. But the regulation just says that we'll ask U.S. EPA and DPR, and they're basically making that call. We're just updating the list.

CHAIRPERSON MACK: In short, yes.

CHIEF COUNSEL MONAHAN-CUMMINGS: Yes.

CHAIRPERSON MACK: So this is an ex officio act that has no a priori meaning for us?

CHIEF COUNSEL MONAHAN-CUMMINGS: Pretty much.

CHAIRPERSON MACK: All right. Based upon the

information you have been provided from U.S. EPA - or by U.S. EPA, if I were writing it -- should the five chemicals noted on Exhibit A be added to the list of chemicals required by State or federal law to be tested, but which have not been adequately tested as required? I, as Chair, then request "yes" votes.

Will everybody who agrees to this proposition signify by raising their hand.

(Hands raised.)

CHAIRPERSON MACK: No? Any noes?

Any abstinence?

Okay. You have got your protocol satisfied.

CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you.

And then they have the second list, Exhibit B.

CHAIRPERSON MACK: Oh, there's the second one.

Based upon the information we have been provided from U.S. EPA and CDPR -- which is the California Department of Pesticide Regulation, I believe.

CHIEF COUNSEL MONAHAN-CUMMINGS: Correct.

CHAIRPERSON MACK: -- should the chemicals noted on Exhibit B be removed from the list of chemicals required by State or federal law to be tested, but which have been adequately tested as required?

The Chair then requests "yes" votes.

Would everybody who agrees to that proposition

raise their hand.

COMMITTEE MEMBER HOPP: I have a comment.

CHAIRPERSON MACK: Okay.

COMMITTEE MEMBER HOPP: This list includes nicotine and its derivatives and malathion. So this takes those drugs off the possible list of --

COMMITTEE MEMBER HAMBURG: No. It's a list of whether it's been tested or not. It's just a list to notify whether it's been tested.

CHAIRPERSON MACK: These are chemicals which we are agreeing to say, because we have been told to do so, that the EPA has, in fact, tested these in satisfaction of State and federal law.

COMMITTEE MEMBER HAMBURG: Not --

CHAIRPERSON MACK: Not that they have anything to do with carcinogenesis.

COMMITTEE MEMBER HAMBURG: Just that the test has been done.

COMMITTEE MEMBER HOPP: I understand. I'm just pointing out what's on the list, because these are not insignificant chemicals.

CHAIRPERSON MACK: Joe.

COMMITTEE MEMBER LANDOLPH: Well, so EPA has done the testing?

CHAIRPERSON MACK: On the second list, EPA has

satisfied itself that the testing has been done. It may not have done it itself.

COMMITTEE MEMBER LANDOLPH: Okay. So if they've done it, they've done it. That's all. It's done.

COMMITTEE MEMBER HAMBURG: That's the question, have they done it?

CHAIRPERSON MACK: I will now re-read --

COMMITTEE MEMBER LANDOLPH: Just so it's clear that it's their responsibility, not ours.

CHAIRPERSON MACK: Based upon the information we have been provided from U.S. EPA and CDPR, should the chemicals noted on Exhibit B be removed from the list of chemicals required by State or federal law to be tested, but which have not been adequately tested as required?

Everybody that agrees to that proposition raise their hand.

(Hands raised.)

CHAIRPERSON MACK: Noes?

And abstinence? No.

So you have got your second proposition satisfied.

CHIEF COUNSEL MONAHAN-CUMMINGS: Thank you very much. I appreciate it.

CHAIRPERSON MACK: Do we have anymore business?

DIRECTOR DENTON: Yes, we do. Staff updates.

CHAIRPERSON MACK: Staff updates. That must be why Martha moved over to that place.

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Yes. I was trying to go through the -- make sure you saw and the audience saw all the pictures.

So if we can open this again.

(Thereupon an overhead presentation was Presented as follows.)

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Okay. So I'm ready to go if you are.

This is an update on prioritization and where we are in applying the epidemiology data screen and the first animal data screen.

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CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: So the prioritization process is shown here on this slide. And I have highlighted the step in the process that we are discussing today. And, that is, performing screens on the candidate chemicals.

Candidate chemicals are those chemicals in our tracking database with data suggesting that they cause cancer and have exposure potential in California. We screen them through focused literature reviews. At your last meeting in November of 2007, we presented the results of applying the epidemiology data screen to candidate

chemicals in our OEHHA tracking database. And two of those chemicals we brought to you today for listing consideration, TNT and dimethylformamide. The third will come to you at your next meeting.

That process, that screening process identified those three chemicals. We also discussed at your last meeting the next steps for prioritization, namely, to screen the candidate chemicals in the database with an epidemiology data screen again, and at the same time to add an animal data screen.

So at your last meeting, we presented two options for possible animal data screens for Committee discussion and input.

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CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: And here they are, if you recall. So at your last meeting, the Committee suggested that we consider merging both the proposed screen 1 and proposed screen 2 into one for use in the next round of screening. So following that advice, OEHHA looked carefully at how we could do that. And we determined that merging the two animal data screens into one would result in a screen that was very time consuming to apply to each candidate chemical, because it would require that focused literature searches and literature reviews be performed covering three types of

information for each individual chemical.

The first type being animal cancer bioassays. The second being information on structurally similar chemicals that are carcinogenic. And the third being mechanistic information.

So as an alternative, OEHHA developed an approach in which focused literature searches and literature reviews are conducted on one type of animal data, namely, the animal cancer bioassay data. What we've done is shown here. This is our animal data screen we're using in 2008.

We are just looking at animal cancer bioassay data in this animal screen. And what our screen does is it identifies chemicals with either two or more positive animal cancer bioassays, with positive bioassays defined as those bioassays reporting an increased incidence of malignant or combined benign and malignant tumors.

And it also picks up chemicals with one positive animal cancer bioassay, in which the tumors occurred to an unusual degree with regard to incidence, site or type of tumor or age at onset; or chemicals with one positive animal bioassay with findings of tumors at multiple sites; or chemicals with one positive animal cancer bioassay and evidence from a second animal study of benign tumors known to progress to malignancy.

So we are currently screening 380 candidate

chemicals in our tracking database.

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CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: This entails reapplying the epidemiology data screen and then applying that 2008 animal data screen. For chemicals that pass either screen, we then conduct a preliminary toxicological evaluation of the overall evidence. And this evaluation includes consideration of the information that we've identified in our screening level preliminary review of available literature on that chemical, such as readily available human data, animal cancer bioassay data, data on mechanisms of action, metabolism and pharmacokinetics and structural similar carcinogens.

Now, this is a screening procedure, so we don't want to spend weeks on one chemical. We want to be able to move through quickly. And to date, we have completed the screening of about a third of the candidate chemicals. And we anticipate bringing the results of this screening effort to you at your May 2009 meeting as the next group of chemicals that are in that group called "proposed for Committee consideration." And I'll take you back to the process.

So right under that box, "Chemicals Proposed for Committee Consideration," we'll bring those to you at your

next meeting.

And that's the end of the update. Any questions?

COMMITTEE MEMBER LANDOLPH: Hi, Martha. I have a question.

So based on a suggestion I made many years ago, and Irva Hertz-Picciotto wrote up again, we thought that it would make sense to try -- and then we had all the prioritization meetings -- we thought it would make sense to use the epidemiology as a screen. But I'm seeing that the epidemiology that's bringing these chemicals forth is not really strong. I mean, the two chemicals we looked at today, the epidemiology was kind of weak on those. So in what you think you have in the tracking database, is the epidemiology about as weak as it was for these two chemicals that we had today?

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Well, you know, we screened a smaller number of chemicals the last time. And we found the three chemicals that we brought forward. But as time goes on, more studies are published. So it's very hard to predict what the strength of the evidence will be, you know. So far in our screening effort, we've identified one new chemical based on the human screen. But we're identifying, you know, many more chemicals on the animal data screen, because we've already screened so many for human data.

COMMITTEE MEMBER LANDOLPH: All right. So then my follow-up question would be: Say, if you only find one, based on epidemiology, but you find a number of them based on animals, what, will you then bring forward, say, one based on the epidemiology and then drop to the animals and bring one or two more forward? Is that how you're going to proceed?

CANCER TOXICOLOGY & EPIDEMIOLOGY SECTION CHIEF SANDY: Actually, we're doing both screens simultaneously -- or sequentially, I should say. And that's consistent with our prioritization document. It was finalized in December of 2004, which your committee approved.

So the idea is that we will just continue to -- as we add a new screen, we'll apply all the old screens. That effort of reapplying a screen doesn't take very long, because we know we completed a screen a couple years back, so we don't have to search the literature for more than a year or two.

COMMITTEE MEMBER LANDOLPH: Thank you.

DIRECTOR DENTON: And, Dr. Landolph, you'll remember that the next stage is we would bring these chemicals to you, we would say, "Okay, here's what that screen says about this. Do you advise that we go forward and prepare hazard identification materials to bring it

back to the Committee or not?" So --

COMMITTEE MEMBER LANDOLPH: Yeah. And I think that's a great idea, because it will save you a lot of work and your staff and hopefully focus on those that are worth having you invest all that labor to prepare the hazard identification document. I think it's a good step.

CHAIRPERSON MACK: Any other alert persons with something to say?

Thank you, Martha.

Are we finished?

DIRECTOR DENTON: No. We have Cindy and then we have Carol.

CHAIRPERSON MACK: All right. Now, Cynthia.

MS. OSHITA: Good afternoon. Since the Committee met last November 2007, OEHHA has administratively added ten chemicals to the Prop 65 list. Seven were added as known to cause cancer. And they include dibromoacetic acid, benthiavalicarb-isopropyl -- excuse my pronunciation here -- mepanipyrim, pirimicarb, resmethrin, gallium arsenide, and oryzalin. And three chemicals were added as known to cause reproductive toxicity. And they include hexafluoracetone, nitrous oxide, and vinyl cyclohexene.

There is a summary sheet included in your binders under the staff updates that will list the chemicals along with their effective listing dates.

In addition to these listings, there are a couple of other chemicals that are under consideration for listing. And they include 4-methylimidazole as a chemical known to cause cancer, and methanol as a chemical known to cause reproductive toxicity. We've received comments on these chemicals and they're currently under review.

Also, included in your binders is a summary sheet of the safe harbor levels that we've adopted during this past year. A no-significant-risk level was adopted for nitromethane. That was effective April 28th, 2008. And for C.I. Direct Blue 218, which was effective September 7th, 2008.

There was also a maximum allowable dose level that was adopted for di-n-butyl phthalate, which was effective July 23rd, 2008. And we have a rulemaking package adopting MADL for di-n-hexyl phthalate that has been submitted to the Office of Administrative Law. And we await the Office's decision of approval within the next month.

Earlier this year, in March, we issued a Notice of Proposed Rulemaking announcing the proposed NSRL for ethylbenzene. We've received written comments, which we are reviewing, and we will respond to them as part of the rulemaking process.

Thank you.

CHAIRPERSON MACK: Thank you.

Carol.

CHIEF COUNSEL MONAHAN-CUMMINGS: All right. In terms of litigation update, I wanted to just give you a couple of notes. One is that this group has kind of been following the litigation that was filed for failure to provide warnings for acrylamide exposures in food. If you recall, this group was involved in a lot of different issues related to providing warnings and things like that for acrylamide. And I just wanted to let you know that the Attorney General's cases that were filed against a number of different companies have all been resolved now. And you may have noticed that some restaurants are providing acrylamide warnings now for exposures for foods. And a number of other companies have agreed to reduce the acrylamide levels in their products, including chips and french fries, to levels that don't require a warning. So I just wanted to let you know that that was the outcome of that litigation. We weren't parties and neither were you in those cases, but it was something of interest to you. Acrylamide is listed as a carcinogen. So there's that one.

And then the other case I'm sure you're all aware of is the Sierra Club versus Schwarzenegger case, in which this group is one of the defendants. And just to give you

a quick update on that. As you know, our -- we had filed a demurrer to the case initially and were unsuccessful, except slightly so for this group in terms of the Court did grant the demurrer in terms of your mandatory duty to list chemicals. But your discretionary duties are still in here. And so, unfortunately for you, you're still defendants in the case.

But that case is moving forward. It's in the very preliminary stages. Some discovery has been exchanged and there is a motion that's pending in the court in Alameda County on December the 9th to determine a -- it's a motion for summary adjudication as to listings under the California Labor Code provision of Prop 65, which you're not involved in in this group. But the allegation is that there are about 92 chemicals that should be listed under Prop 65 as either carcinogens or reproductive toxicants that haven't been -- so that motion will be heard in December. And following the outcome of that we'll certainly let you know what's happening with the case. But there is no trial date set yet for this case.

CHAIRPERSON MACK: Thank you.

DIRECTOR DENTON: I'd like to summarize then what's happened today. By a vote of 3 yes and 4 no, the Committee has decided not to list Dimethylformamide. But

by a unanimous vote, the Committee has listed TNT.

Also, by unanimous vote, the Committee updated the Section 24000 list as recommended by staff.

CHIEF COUNSEL MONAHAN-CUMMINGS: 27000.

DIRECTOR DENTON: 27000.

I would just like to say that how much we, and I, and I think the panel appreciate the work that's been done by the staff of OEHHA. These meetings are quite time consuming and also labor intensive. And so I want to say how much that I, as the Director, appreciate the work that's done by my staff. And if I could just mention them: Jay Beaumont and Martha Sandy and Susan Luong and Allen Hirsh and Kate Li and George Alexeeff and Cindy, Susan, Lindsey, Fran. Amy Dunn was here earlier. Lauren, Carol. I don't think I missed anybody.

Of course, Dave Morry sitting in the back.

And I also, on behalf of OEHHA, would like to thank the due diligence and the commitment of this panel and for participating in the work of Prop 65. And we're always very impressed with the quality of the discussions and the commitment and the carefulness with which you consider the work that you do. So with that, I'd like to say thank you very much. And I guess Happy Thanksgiving, Happy Holidays, and Happy New Year, and we'll see you next year.

CHAIRPERSON MACK: Happy New Administration.

(Thereupon the Carcinogen Identification Committee adjourned at 2:52 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Office of Environmental Health Hazard Assessment, Carcinogen Identification Committee was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said workshop nor in any way interested in the outcome of said workshop.

IN WITNESS WHEREOF, I have hereunto set my hand this 13th day of November, 2008.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
License No. 10063